

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<p>(51) International Patent Classification ⁶ : C07D 261/20, 275/04, A61K 31/42, 31/425, C07D 263/56, 231/56, 249/18, 239/74, A61K 31/505, 31/415, 31/41</p>	<p>A1</p>	<p>(11) International Publication Number: WO 97/28137 (43) International Publication Date: 7 August 1997 (07.08.97)</p>
<p>(21) International Application Number: PCT/US97/01749 (22) International Filing Date: 31 January 1997 (31.01.97) (30) Priority Data: 60/011,080 2 February 1996 (02.02.96) US 9604234.6 28 February 1996 (28.02.96) GB 60/034,434 23 December 1996 (23.12.96) US (71) Applicant (for all designated States except US): MERCK & CO., INC. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): ADAMS, Alan, D. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). BERGER, Joel, P. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). BERGER, Gregory, D. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). FITCH, Kenneth, J. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). GRAHAM, Donald, W. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). JONES, Anthony, B. [GB/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). VON LANGEN, Derek [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US).</p>		<p>(US). LEIBOWITZ, Mark, D. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). MOLLER, David, E. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). PATCHETT, Arthur, A. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). SANTINI, Conrad [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). SAHOO, Soumya, P. [IN/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). TOLMAN, Richard, L. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). TOUPENCE, Richard, B. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). WALSH, Thomas, F. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). (74) Common Representative: MERCK & CO., INC.; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). (81) Designated States: AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, EE, GE, HU, IL, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TJ, TM, TR, TT, UA, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i></p>
<p>(54) Title: HETEROCYCLIC DERIVATIVES AS ANTIDIABETIC AND ANTIOBESITY AGENTS (57) Abstract The instant invention is concerned with acetylphenols which are useful as antiobesity and antidiabetic compounds. Compositions and methods for the use of the compounds in the treatment of diabetes and obesity and for lowering or modulating triglyceride levels and cholesterol levels or raising high density lipoprotein levels or for increasing gut motility or for treating atherosclerosis are also disclosed.</p>		

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AM	Armenia	GB	United Kingdom	MW	Malawi
AT	Austria	GE	Georgia	MX	Mexico
AU	Australia	GN	Guinea	NE	Niger
BB	Barbados	GR	Greece	NL	Netherlands
BE	Belgium	HU	Hungary	NO	Norway
BF	Burkina Faso	IE	Ireland	NZ	New Zealand
BG	Bulgaria	IT	Italy	PL	Poland
BJ	Benin	JP	Japan	PT	Portugal
BR	Brazil	KE	Kenya	RO	Romania
BY	Belarus	KG	Kyrgyzstan	RU	Russian Federation
CA	Canada	KP	Democratic People's Republic of Korea	SD	Sudan
CF	Central African Republic	KR	Republic of Korea	SE	Sweden
CG	Congo	KZ	Kazakhstan	SG	Singapore
CH	Switzerland	LI	Liechtenstein	SI	Slovenia
CI	Côte d'Ivoire	LK	Sri Lanka	SK	Slovakia
CM	Cameroon	LR	Liberia	SN	Senegal
CN	China	LT	Lithuania	SZ	Swaziland
CS	Czechoslovakia	LU	Luxembourg	TD	Chad
CZ	Czech Republic	LV	Latvia	TG	Togo
DE	Germany	MC	Monaco	TJ	Tajikistan
DK	Denmark	MD	Republic of Moldova	TT	Trinidad and Tobago
EE	Estonia	MG	Madagascar	UA	Ukraine
ES	Spain	ML	Mali	UG	Uganda
FI	Finland	MN	Mongolia	US	United States of America
FR	France	MR	Mauritania	UZ	Uzbekistan
GA	Gabon			VN	Viet Nam

HETEROCYCLIC DERIVATIVES AS ANTIDIABETIC AND ANTI OBESITY AGENTS

This application is a continuation-in part and claims priority to of each of the following U.S provisional applications: application no. 60/011080 filed February 2, 1996 (Merck attorney docket no. 19632PV); and application no. 60/----- filed December 23, 1996 (Merck attorney docket no. 19632PV2); each of which are herein incorporated by reference in their entirety.

This application is related to the following U.S. non-provisional applications: Serial No. --/----- filed January 31, 1997 (Merck attorney docket no. 19869Y) which is herein incorporated by reference in its entirety.

BACKGROUND OF THE INVENTION

Diabetes refers to a disease process derived from multiple causative factors and characterized by elevated levels of plasma glucose or hyperglycemia. Uncontrolled hyperglycemia is associated with increased and premature mortality due to an increased risk for microvascular and macrovascular diseases, including nephropathy, neuropathy, retinopathy, hypertension, stroke, and heart disease. Therefore, control of glucose homeostasis is a critically important approach for the treatment of diabetes.

Type I diabetes (IDDM) is the result of an absolute deficiency of insulin, the hormone which regulates glucose utilization. Type II, noninsulin dependent diabetes mellitus (NIDDM) is due to a profound resistance to insulin stimulating or regulatory effect on glucose and lipid metabolism in the main insulin-sensitive tissues, muscle, liver and adipose tissue. This resistance to insulin responsiveness results in insufficient insulin activation of glucose uptake, oxidation and storage in muscle and inadequate insulin repression of lipolysis in adipose tissue and of glucose production and secretion in liver.

The several treatments for NIDDM, which has not changed substantially in many years, are all with limitations. While physical

- 2 -

exercise and reductions in dietary intake of calories will dramatically improve the diabetic condition, compliance with this treatment is very poor because of well-entrenched sedentary lifestyles and excess food consumption, especially high fat-containing food. Increasing the plasma level of insulin by administration of sulfonylureas (e.g. tolbutamide, glipizide) which stimulate the pancreatic β -cells to secrete more insulin or by injection of insulin after the response to sulfonylureas fails, will result in high enough insulin concentrations to stimulate the very insulin-resistant tissues. However, dangerously low levels of plasma glucose can result from these last two treatments and increasing insulin resistance due to the even higher plasma insulin levels could theoretically occur. The biguanides increase insulin sensitivity resulting in some correction of hyperglycemia. However, the two biguanides, phenformin and metformin, can induce lactic acidosis and nausea/diarrhea, respectively.

Thiazolidinediones (glitazones) are a recently disclosed class of compounds that are suggested to ameliorate many symptoms of NIDDM. These agents increase insulin sensitivity in muscle, liver and adipose tissue in several animal models of NIDDM resulting in complete correction of the elevated plasma levels of glucose, triglycerides and nonesterified free fatty acids without any occurrence of hypoglycemia. However, serious undesirable effects have occurred in animal and/or human studies including cardiac hypertrophy, hemadilution and liver toxicity resulting in few glitazones progressing to advanced human trials.

Hyperlipidemia is a condition which is characterized by an abnormal increase in serum lipids, such as cholesterol, triglycerides and phospholipids. These lipids do not circulate freely in solution in plasma, but are bound to proteins and transported as macromolecular complexes called lipoproteins. See the *Merck Manual*, 16th Ed. 1992 (see for example pp. 1039-1040) and "Structure and Metabolism of Plasma Lipoproteins" in *Metabolic Basis of Inherited Disease*, 6th Ed. 1989, pp. 1129-1138. One form of hyperlipidemia is hypercholesterolemia, characterized by the existence of elevated LDL cholesterol levels. The

- 3 -

initial treatment for hypercholesterolemia is often to modify the diet to one low in fat and cholesterol, coupled with appropriate physical exercise, followed by drug therapy when LDL-lowering goals are not met by diet and exercise alone. LDL is commonly known as the "bad" cholesterol, while HDL is the "good" cholesterol. Although it is desirable to lower elevated levels of LDL cholesterol, it is also desirable to increase levels of HDL cholesterol. Generally, it has been found that increased levels of HDL are associated with lower risk for coronary heart disease (CHD). See, for example, Gordon, et al., *Am. J. Med.*, 62, 707-714 (1977); Stampfer, et al., *N. England J. Med.*, 325, 373-381 (1991); and Kannel, et al., *Ann. Internal Med.*, 90, 85-91 (1979). An example of an HDL raising agent is nicotinic acid, but the quantities needed to achieve HDL raising are associated with undesirable effects, such as flushing.

It is suggested that thiazolidinedione compounds exert their effects by binding to the peroxisome proliferator activated receptor (PPAR) family of receptors, controlling certain transcription elements having to do with the biological entities listed above. See Hulin et al., *Current Pharm. Design* (1996) 2, 85-102. Three sub-types of PPARs have been discovered and described; they are PPAR α , PPAR γ and PPAR δ . PPAR α is activated by a number of medium and long-chain fatty acids, and it is involved in stimulating β -oxidation of fatty acids. PPAR α is also involved with the activity of fibrates in rodents and humans. Fibric acid derivatives such as clofibrate, fenofibrate, bezafibrate, ciprofibrate, beclofibrate and etofibrate, as well as gemfibrozil, produce a substantial reduction in plasma triglycerides along with moderate reduction in LDL cholesterol, and they are used particularly for the treatment of hypertriglyceridemia.

The PPAR γ receptor subtypes are involved in activating the program of adipocyte differentiation and are not involved in stimulating peroxisome proliferation in the liver. The DNA sequences for the PPAR γ receptors are described in Elbrecht, et al., *BBRC* 224;431-437 (1996). Although peroxisome proliferators, including the fibrates and fatty acids, activate the transcriptional activity of PPAR's, only

- 4 -

prostaglandin J₂ derivatives have been identified as natural ligands of the PPAR γ subtype, which also binds thiazolidinedione antidiabetic agents with high affinity. The glitazones have been shown to bind exclusively to the PPAR γ subtype.

The human nuclear receptor gene PPAR δ (hPPAR δ) has been cloned from a human osteosarcoma cell cDNA library and is fully described in A. Schmidt et al., *Molecular Endocrinology*, 6 :1634-1641 (1992), herein incorporated by reference. It should be noted that PPAR δ is also referred to in the literature as PPAR β and as NUC1, and each of these names refers to the same receptor; in Schmidt et al, the receptor is referred to as NUC1.

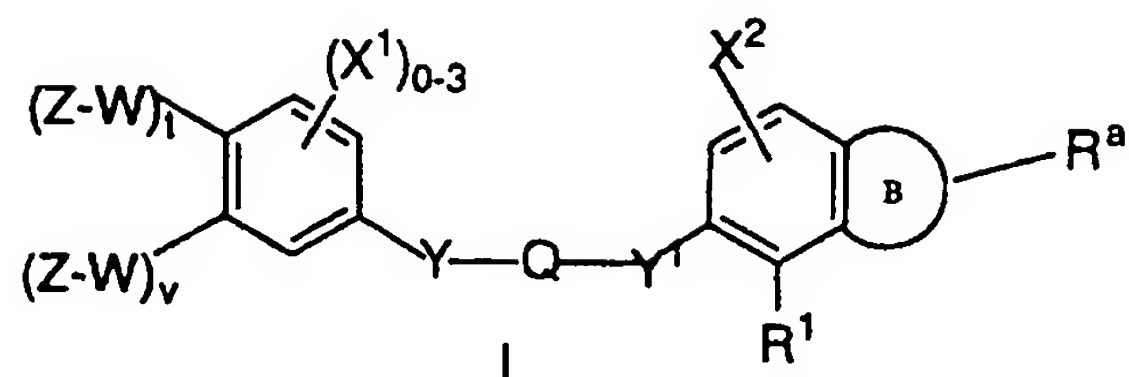
SUMMARY OF THE INVENTION

This invention is concerned with the compounds of formula I below and its analogs, pharmaceutically acceptable salts thereof, and bioprecursors thereof, which differ from the thiazolidinediones in that they lack the thiazolidinedione moiety and they do not lead to the array of toxicity's associated with the thiazolidinediones. The instant compounds are effective in treating diabetes, atherosclerosis, hyperglycemia, hyperlipidemia and/or obesity because they lower one or more of the following biological entities in mammals; glucose, insulin, triglycerides, fatty acids, cholesterol and the like. Thus, it is an object of this invention to describe such compounds. It is a further object to describe the specific preferred stereoisomers of the substituted compounds. A still further object is to describe processes for the preparation of such compounds. Another object is to describe methods and compositions which use the compounds as the active ingredient thereof. Further objects will become apparent from reading the following description.

DESCRIPTION OF THE INVENTION

The present invention is directed to a compound represented by formula I:

- 5 -



or a pharmaceutically acceptable salt thereof, wherein:

R is selected from the group consisting of H, C₁₋₆ alkyl, C₅₋₁₀ aryl, and C₅₋₁₀ heteroaryl, said alkyl, aryl and heteroaryl optionally substituted with 1 to 3 groups of R^a;

R¹ is selected from a group consisting of: H, C₁₋₁₅ alkyl, C₂₋₁₅ alkenyl, C₂₋₁₅ alkynyl and C₃₋₁₀ cycloalkyl, said alkyl, alkenyl, alkynyl, and cycloalkyl optionally substituted with 1 to 3 groups of R^a;

R³ is selected from a group consisting of: H, NHR¹, NHacyl, C₁₋₁₅ alkyl, C₃₋₁₀ cycloalkyl, C₂₋₁₅ alkenyl, C₁₋₁₅ alkoxy, CO₂alkyl, OH, C₂₋₁₅ alkynyl, C₅₋₁₀ aryl, C₅₋₁₀ heteroaryl said alkyl, cycloalkyl, alkenyl, alkynyl, aryl and heteroaryl optionally substituted with 1 to 3 groups of R^a;

(Z-W-) is Z-CR⁶R⁷-, Z-CH=CH-, or $Z-\overset{\overset{R^6}{\diagup}}{\underset{\diagdown}{C}}-R^8-$;

R⁸ is selected from the group consisting of CR⁶R⁷, O, NR⁶, and S(O)_p;

R⁶ and R⁷ are independently selected from the group consisting of H, C₁₋₆ alkyl;

B is a 5 or 6 membered heterocycle containing 0 to 2 double bonds, and 2 heteroatoms independently selected from the group consisting of O, N and S, said heteroatoms are optionally substituted at any position on the

- 6 -

five or six membered heterocycle, the heterocycle being optionally unsubstituted or substituted with 1 to 3 groups of R^a ;

X^1 and X^2 are independently selected from a group consisting of: H, OH, C₁₋₁₅ alkyl, C₂₋₁₅ alkenyl, C₂₋₁₅ alkynyl, halo, OR^3 , $ORCF_3$, C₅₋₁₀ aryl, C₅₋₁₀ aralkyl, C₅₋₁₀ heteroaryl and C₁₋₁₀ acyl, said alkyl, alkenyl, alkynyl, aryl and heteroaryl optionally substituted with 1 to 3 groups of R^a ;

R^a represents a member selected from the group consisting of: halo, acyl, aryl, heteroaryl, CF_3 , OCF_3 , CN, NO_2 , R^3 , OR^3 , SR^3 , $S(O)R^3$, $=N(OR)$, SO_2R^3 , NR^3R^3 , NR^3COR^3 , $NR^3CO_2R^3$, $NR^3CON(R^3)_2$, $NR^3SO_2R^3$, COR^3 , CO_2R^3 , $CON(R^3)_2$, $SO_2N(R^3)_2$, $OCON(R^3)_2$ said aryl and heteroaryl optionally substituted with 1 to 3 groups of halo or C₁₋₆ alkyl;

Y is selected from the group consisting of: $S(O)_p$, $-CH_2-$, $-C(O)-$, $-C(O)NH-$, $-NR-$, $-O-$, $-SO_2NH$, $-NHSO_2$;

Y^1 is selected from the group consisting of: O and C;

Z is selected from the group consisting of: CO_2R^3 , $CONHSO_2R$, $CONH_2$ and 5-(1H-tetrazole);

t and v are independently 0 or 1 such that $t + v = 1$;

Q is a saturated or unsaturated straight chain hydrocarbon containing 2-4 carbon atoms and

p is 0-2.

Included in the invention is a pharmaceutical composition which is comprised of a compound of formula I in combination with a pharmaceutically acceptable carrier.

- 7 -

Also included in the invention is a pharmaceutical composition which is comprised of a compound of formula I in combination with one or more known sulfonylureas, biguanides, α -glucosidase inhibitors, other insulin secretagogues as well as insulin.

Also included in the invention is a method for raising high density lipoprotein (HDL) plasma levels in a mammal in need of such treatment comprising administering an effective amount of a compound of formula I.

Also included in the invention is a method for preventing, halting or slowing the progression of atherosclerotic cardiovascular diseases and related conditions and disease events in a mammal in need of such treatment comprising administering an effective amount of a compound of formula I.

Also included in the invention is a method for preventing, halting or slowing the progression of atherosclerotic cardiovascular diseases and related conditions and disease events in a mammal in need of such treatment comprising administering an effective amount of a compound of formula I in combination with one or more active agents such as antihyperlipidemic agents, HMG-CoA synthase inhibitors, squalene epoxidase inhibitors and the like..

Also included in the invention is a method of treating or controlling diabetes, which comprises administering to a diabetic patient an effective amount of a compound of formula I.

Also included in the invention is a method of treating or controlling diabetes, which comprises administering a compound of formula I in combination with one or more known sulfonylureas, biguanides, α -glucosidase inhibitors, other insulin secretagogues as well as insulin.

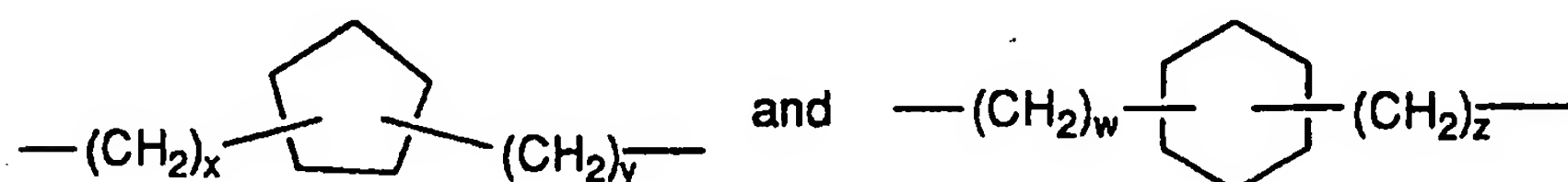
The invention is described herein in detail using the terms defined below unless otherwise specified.

The term "alkyl" refers to a monovalent alkane (hydrocarbon) derived radical containing from 1 to 15 carbon atoms unless otherwise defined. It may be straight, branched or cyclic. Preferred straight or branched alkyl groups include methyl, ethyl,

- 8 -

propyl, isopropyl, butyl and t-butyl. Preferred cycloalkyl groups include cyclopentyl and cyclohexyl.

Alkyl also includes a straight or branched alkyl group which contains or is interrupted by a cycloalkylene portion. Examples include the following:



wherein: x and y = from 0-10; and w and z = from 0-9.

The alkylene and monovalent alkyl portion(s) of the alkyl group can be attached at any available point of attachment to the cycloalkylene portion.

When substituted alkyl is present, this refers to a straight, branched or cyclic alkyl group as defined above, substituted with 1-3 groups as defined with respect to each variable.

The term "alkenyl" refers to a hydrocarbon radical straight, branched or cyclic containing from 2 to 15 carbon atoms and at least one carbon to carbon double bond. Preferably one carbon to carbon double bond is present, and up to four non-aromatic (non-resonating) carbon-carbon double bonds may be present. Preferred alkenyl groups include ethenyl, propenyl, butenyl and cyclohexenyl. As described above with respect to alkyl, the straight, branched or cyclic portion of the alkenyl group may contain double bonds and may be substituted when a substituted alkenyl group is provided.

The term "alkynyl" refers to a hydrocarbon radical straight, branched or cyclic, containing from 2 to 15 carbon atoms and at least one carbon to carbon triple bond. Up to three carbon-carbon triple bonds may be present. Preferred alkynyl groups include ethynyl, propynyl and butynyl. As described above with respect to alkyl, the straight, branched or cyclic portion of the alkynyl group may contain

- 9 -

triple bonds and may be substituted when a substituted alkynyl group is provided.

The term "alkoxy" refers to those groups of the designated carbon length in either a straight or branched configuration attached through an oxygen linkage and if two or more carbon atoms in length, they may include a double or a triple bond. Exemplary of such alkoxy groups are methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, tertiary butoxy, pentoxy, isopentoxy, hexoxy, isohexoxy allyloxy, propargyloxy, and the like.

The term halo as used herein, represents fluoro, chloro, bromo or iodo.

Aryl refers to aromatic rings e.g., phenyl, substituted phenyl and like groups as well as rings which are fused, e.g., naphthyl and the like. Aryl thus contains at least one ring having at least 5 atoms, with up to two such rings being present, containing up to 10 atoms therein, with alternating (resonating) double bonds between adjacent carbon atoms. The preferred aryl groups are phenyl and naphthyl. Aryl groups may likewise be substituted with 0-3 groups selected from R^a . The preferred aryl groups are phenyl and naphthyl. Aryl groups may likewise be substituted as defined below. Preferred substituted aryls include phenyl and naphthyl substituted with zero or three groups of R^a .

Heteroaryl is a group containing from 5 to 10 atoms, 1-4 of which are heteroatoms, 0-4 of which heteroatoms are N and 0-1 of which are O or S, said heteroaryl group being unsubstituted or substituted with 0-3 R^a groups; examples of heteroaryls are pyridyl, quinolyl, purinyl, imidazolyl, imidazopyridyl and pyrimidinyl.

One embodiment of the novel compounds of the instant invention is realized when:

Y is O and all other variables are described as above.

Another embodiment of the novel compounds of the instant invention is realized when:

Y is $S(O)_p$, p is 0-2 and all other variables are described as above.

- 10 -

Still another embodiment of the novel compounds of the instant invention is realized when:

Y is -CH₂- and all other variables are described as above.

Yet another embodiment of the novel compounds of the instant invention is realized when:

Y is CO and all other variables are described as above.

A further embodiment of the novel compounds of the instant invention is realized when:

Y is NR and all other variables are described as above.

Another embodiment of the novel compounds of the instant invention is realized when:

Y is NHSO₂ or SO₂NH and all other variables are described as above.

Another embodiment of the novel compounds of the instant invention is realized when:

Y is -C(O)NH- and all other variables are described as above.

Another embodiment of the novel compounds of the instant invention is realized when:

B is a 5 or 6 membered heterocycle containing 0 to 2 double bonds, and 2 heteroatoms G and J, which are substituted at any position on the five or six membered heterocycle, the heterocycle being optionally unsubstituted or substituted with 1 to 3 groups of R^a and all other variables are described as above.

Another embodiment of the novel compounds of the instant invention is realized when:

(Z-W-) is Z-CR⁶R⁷-, Z-CH=CH-, or
$$\begin{array}{c} \text{R}^6 \quad \text{R}^7 \\ \diagdown \quad \diagup \\ \text{Z}-\text{C}-\text{R}^8- \end{array};$$
 and all other variables are described as above and all other variables are described as above.

Still another embodiment of the novel compounds of the instant invention is realized when:

(Z-W-) is Z-CR⁶R⁷- or
$$\begin{array}{c} \text{R}^6 \quad \text{R}^7 \\ \diagdown \quad \diagup \\ \text{Z}-\text{C}-\text{R}^8- \end{array};$$

- 11 -

and all other variables are described as above and all other variables are described as above.

Another embodiment of the novel compounds of the instant invention is realized when: R^a is selected from the group consisting of C1-6 alkyl, CF_3 , aryl, halo, acyl, OCF_3 , $-NO_2$, OR^3 ; COR^3 , CO_2R^3 , $CON(R^3)_2$, and $SO_2N(R^3)_2$; and $X1$ is selected from the group consisting of H, OH, C1-6 alkyl, C2-15 alkenyl, halo and OR^3 and all other variables are described as above.

Another preferred embodiment of the novel compounds of the instant invention is realized when:
 R is C1-6 alkyl or C5-10 aryl, said alkyl or aryl optionally substituted with 1 to 3 groups of R^a ;

R^1 is C1-15 alkyl;

X^1 & X^2 are independently H, C1-6 alkyl or halo;

Y is O, NH or S;

Y^1 is O;

(Z-W-) is $Z-CR^6R^7-$ or $Z-C(R^6)(R^7)-R^8-$;

R^a is a member selected from the group consisting of: halo, acyl, aryl, heteroaryl, CF_3 , OCF_3 , $-O-$, CN, NO_2 , R^3 , OR^3 ; SR^3 , $S(O)R^3$, SO_2R^3 , NR^3COR^3 , COR^3 , $CON(R^3)_2$, $SO_2N(R^3)_2$, said aryl and heteroaryl optionally substituted with 1 to 3 groups of halo or C1-6 alkyl; and

Z is CO_2R^3 , $CONHSO_2R$, $CONH_2$ or 5-(1H-tetrazole).

- 12 -

Examples of the compounds of the instant invention are:

Methyl 3-chloro-4-(3-(3-ethyl-7-propyl-6-benz-[4,5]-isoxazoloxy)-propylthio)phenylacetate;

3-chloro-4-(3-(3-ethyl-7-propyl-6-benz-[4,5]-isoxazoloxy)propylthio)-phenylacetic acid;

Methyl 3-chloro-4-(3-(3-methoxy-7-propyl-6-benz-[4,5]-isoxazoloxy)-propylthio)phenylacetate;

3-chloro-4-(3-(3-methoxy-7-propyl-6-benz-[4,5]-isoxazoloxy)propylthio)-phenylacetic acid;

Methyl 3-chloro-4-(3-(3-ethyl-7-propyl-6-benz-[4,5]-isothiazoloxy)-propylthio)phenyl acetate;

3-chloro-4-(3-(3-ethyl-7-propyl-6-benz-[4,5]-isothiazole)oxy)propylthio phenylacetic acid;

Methyl 3-chloro-4-(3-(3-methyl-7-propyl-6-benz-[4,5]-isoxazoloxy)-propylthio)phenylacetate;

3-chloro-4-(3-(3-methyl-7-propyl-6-benz-[4,5]-isoxazoloxy)propylthio)-phenylacetic acid;

Methyl 3-chloro-4-(3-(3,7-dipropyl-6-benz-[4,5]-isoxazoloxy)propylthio)-phenylacetate;

3-chloro-4-(3-(3,7-dipropyl-6-benz-[4,5]-isoxazoloxy)propylthio) phenyl-acetic acid;

Methyl 3-chloro-4-(3-(3-ethyl-7-propyl-6-benz-[4,5]-isoxazoloxy)-propylthio)phenylacetate S-oxide;

- 13 -

3-chloro-4-(3-(3-ethyl-7-propyl-6-benz-[4,5]-isoxazoloxy)propylthio)-phenylacetic acid S-oxide;

Methyl 3-chloro-4-(3-(3-ethyl-7-propyl-6-benz-[4,5]-isoxazoloxy)propyl-thio)phenylacetate S,S-dioxide;

3-Chloro-4-(3-(3-ethyl-7-propyl-6-benz-[4,5]-isoxazole)oxy)-propylthio phenylacetic acid S,S-dioxide;

tert-Butyl 3-chloro-4-(3-(3-ethyl-7-propyl-6-benz-[4,5]-isoxazoloxy)-propylthio)phenyl acetate;

2-methyl-2-(3-chloro-4-(3-(3-phenyl-7-propylbenz[4,5]isoxazol-6-oxy)propyl)thio)phenyl propionic acid;

Methyl 3-chloro-4-(3-(3-(2,2-dimethylpropyl)-7-propyl-6-benz-[4,5]-isoxazoloxy)-propylamino)phenylacetate;

3-Chloro-4-(3-(3-(2,2-dimethylpropyl)-7-propyl-6-benz-[4,5]-isoxazoloxy)-propylamino)phenylacetic acid;

3-Chloro-4-(3-(2-phenyl-6-propyl-5-benz-[4,7]-oxazoloxy)propylthio)phenylacetic acid;

Methyl 3-propyl-4-(3-(3-trifluoromethyl-7-propyl-6-benz-[4,5]-isoxazoloxy)-propylthio)phenylacetate;

3-propyl-4-(3-(3-trifluoromethyl-7-propyl-6-benz-[4,5]-isoxazoloxy)-propylthio)phenylacetic acid;

3-chloro-4-(3-(2-propyl-3-trifluoromethyl-6-benz-[4,5]-isoxazoloxy)propylthio)phenylacetic acid;

- 14 -

3-chloro-4-(3-(3-phenyl-7-cyclopropylmethyl-6-benz-[4,5]-isoxazoloxy)-butyloxy)phenylacetic acid;

4-(3-(3-Phenyl-7-propylbenzisoxazol-6-yloxy)propylthio)-phenyl(2,2-dimethyl)acetic acid;

3-(3-(3-Phenyl-7-propylbenz[c]pyrazol-6-yloxy)propylamino)-phenyl(2,2-dimethyl)acetic acid;

4-(3-(3-Phenyl-7-propylbenz[c]pyrazol-6-yloxy)propylamino)-phenyl(2,2-dimethyl)acetic acid;

4-(3-(3-Phenyl-7-propylbenzisoxazol-6-yloxy)propyloxy)-phenylpropan-3-oic acid;

4-(4-(3-Phenyl-7-propylbenz[c]pyrazol-6-yloxy)butylamino)-phenylpropan-3-oic acid;

3-(3-(3-Phenyl-7-propylbenzisoxazol-6-yloxy)propylthio)-phenoxyacetic acid;

4-(3-(3-Phenyl-7-propylbenzisoxazol-6-yloxy)propylthio)-phenoxyacetic acid;

4-(4-(1-Phenyl-4-propylbenz[d]triazol-5-yloxy)butyloxy)-phenoxyacetic acid;

N-[4-(3-(3-Phenyl-7-propylbenzisoxazol-6-yloxy)propylamino)-phenyl]glycine;

N-[3-(4-(4-Phenyl-8-propylquinazolin-7-yloxy)butyloxy)-phenyl]glycine;

- 15 -

N-[4-(4-(4-Phenyl-8-propylquinazolin-7-yloxy)butyloxy)-phenyl]glycine;

4-(3-(3-Phenyl-7-propylbenzisoxazol-6-yloxy)propylamino)-phenylacetic acid;

4-(3-(4-Phenyl-8-propylquinazolin-7-yloxy)propylthio)-phenylacetic acid;

3-(3-(2-Phenyl-6-propylbenzoxazol-5-yloxy)propylamino)-3-chlorophenylacetic acid;

4-(3-(2-Phenyl-6-propylbenzoxazol-5-yloxy)propylamino)-3-chlorophenylacetic acid;

4-(3-(2-Phenyl-6-propylbenzoxazol-5-yloxy)propylamino)-phenylacetic acid;

3-(3-(2-Phenyl-5-propylbenzisoxazol-6-yloxy)propylamino)-3-chlorophenylacetic acid;

4-(3-(1-Phenyl-4-propylbenz[d]triazol-5-yloxy)propylamino)-3-chlorophenylacetic acid;

3-(3-(3-Phenyl-7-propylbenz[c]pyrazol-6-yloxy)propylamino)-3-chlorophenylacetic acid;

4-(3-(3-Phenyl-7-propylbenzisoxazol-6-yloxy)propylamino)-3-chlorophenylacetic acid;

4-(4-(3-Phenyl-7-prop-2-enylbenzisoxazol-6-yloxy)butyloxy)-3-chlorophenylacetic acid;

- 16 -

4-(3-(3-Phenyl-7-propylbenzisoaxazol-6-yloxy)propylamino)-
phenoxyacetic acid;

3-(3-(3-Phenyl-7-butylbenzisoaxazol-6-yloxy)propylthio)-phenylpropan-
3-oic acid;

4-(3-(3-Phenyl-7-butylbenzisoaxazol-6-yloxy)propylthio)-phenylpropan-
3-oic acid;

4-(3-(3-Phenyl-7-propylbenzisoaxazol-6-yloxy)propyloxy)-2-phenyl-2,2-
dimethylacetic acid;

4-(4-(3-Phenyl-7-(cyclopropylmethyl)benzisoaxazol-6-
yloxy)butylamino)-phenoxy-2,2-dimethylacetic acid;

3-(3-(3-Neopentyl-7-propylbenzisoaxazol-6-yloxy)propylthio)-3-
methylphenylacetic acid

4-(3-(3-(2-Phenyl-2,2-dimethyl)-7-propylbenzisoaxazol-6-
yloxy)propyloxy)-3-butylphenylacetic acid;

4-(3-(3-Chloro-7-propylbenzisoaxazol-6-yloxy)propylamino)-2-
propylphenylacetic acid;

3-(3-(3-Chloro-7-propylbenzisoaxazol-6-yloxy)propylamino)-2-
propylphenylacetic acid;

4-(4-(3-Butoxy-7-propylbenzisoaxazol-6-yloxy)butylthio)-2-
fluorophenylacetic acid;

4-(3-(3-Phenyl-7-propylbenzisoaxazol-6-yloxy)propylamino)-
phenoxyacetic acid;

- 17 -

3-(3-(3-(3-Butylphenyl)-7-butylbenzisoxazol-6-yloxy)propylthio)-phenylpropan-3-oic acid;

4-(3-(3-(2-Tolyl)-7-butylbenzisoxazol-6-yloxy)propylthio)-phenylpropan-3-oic acid;

4-(3-(3-(4-Fluorophenyl)-7-propylbenzisoxazol-6-yloxy)propyloxy)-2-phenyl-2,2-dimethylacetic acid;

4-(3-(3-Phenyl-7-propylbenzisoxazol-6-yloxy)propyloxy)-phenoxy-2-*spiro*-cyclopropylacetic acid;

3-(3-(3-Phenyl-7-propylbenzisoxazol-6-yloxy)propyloxy)-phenoxy-2-*spiro*-cyclopropylacetic acid;

5-(4-(3-(3-Phenyl-7-propylbenz[c]pyrazol-6-yloxy)propylamino)phenyl-2-(2,2-dimethyl)-ethyl)-tetrazole;

5-(4-(3-(3-Phenyl-7-propylbenzisoxazol-6-yloxy)propyloxy)phenyl-3-propyl)-tetrazole;

5-(4-(4-(1-Phenyl-4-propylbenz[d]triazol-5-yloxy)butylamino)phenyl-3-propyl)-tetrazole;

5-(3-(3-(3-Phenyl-7-propylbenzisoxazol-6-yloxy)propylthio)phenoxy-2-ethyl)-tetrazole;

5-(4-(3-(3-Phenyl-7-propylbenzisoxazol-6-yloxy)propylthio)phenoxy-2-ethyl)-tetrazole;

3-chloro-4-(3-(3-ethyl-7-propyl-6-benz-[4,5]-isoxazoloxy)-but-2-en-thio)phenylacetic acid;

4-(3-(3-ethyl-7-propyl-6-benz[4,5]isoxazole)oxy)propyloxy phenoxy acetic acid;

- 18 -

N-Methylsulfonyl 3-chloro-4-(3-(3-ethyl-7-propyl-6-benz[4,5]isoxazole)oxy)propylthio phenyl acetamide;

3,5-dimethoxy-4-(3-(3-(Ethyl)-7-(propyl)-6-benz-[4,5]-isoxazoloxy)-propyloxy)phenyl acetic acid;

3,5-dichloro-4-(3-(3-(Ethyl)-7-(propyl)-6-benz-[4,5]-isoxazoloxy)-propyloxy)phenyl acetic acid;

3,5-dimethyl-4-(3-(3-(Ethyl)-7-(propyl)-6-benz-[4,5]-isoxazoloxy)-propyloxy)phenyl acetic acid;

4-(3-(3-(Ethyl)-7-(propyl)-6-benz-[4,5]-isoxazoloxy)-propyloxy)-phenyl propionic acid;

3-chloro-4-(3-phenylmethyl-7-(n-propyl)-6-benz[4,5]isoxazoloxy)propyl-thio)phenylacetic acid;

3-chloro-4-(3-(2,2-dimethylpropyl)-7-(n-propyl)-6-benz[4,5]isoxazoloxy)-propylthio)phenylacetic acid;

2-methyl-4-(3-(3-(Ethyl)-7-(propyl)-6-benz-[4,5]-isoxazoloxy)propyloxy)-phenyl propionic acid;

3-Propyl-4-(3-(3-ethyl-7-propyl-6-benz-[4,5]-isoxazoloxy)-propyloxy)phenylacetic acid;

4-(3-(3-(Ethyl)-7-propyl-6-benz-[4,5]-isoxazoloxy)butyl)phenylacetate;

3-chloro-4-(7-(n-propyl)-3-(3,3,3-trifluoropropyl)-6-benz[4,5]isoxazoloxy)propylthio)phenylacetic acid;

- 19 -

3-chloro-4-(3-(4-chlorophenylmethyl)-7-(n-propyl)-6-benz[4,5]isoxazol-oxy)propylthio)phenylacetic acid;

3-Chloro-4-(3-(3-(2,2-dimethylpropyl)-7-propyl-6-benz-[4,5]-isoxazoloxy)propyl- N-methylamino)phenylacetate;

3,5-Dipropyl-4-(3-(3-ethyl-7-propyl-6-benz-[4,5]-isoxazoloxy)-propyloxy)phenylacetic acid;

3-fluoro-4-(3-(7-propyl-3-trifluoromethyl-6-benz-[4, 5]isoxazoloxy)-propyloxy)phenylacetic acid;

3-chloro-4-(3-(3-trifluoromethyl-7-propyl-6-benz-[4, 5]-isoxazoloxy)propylamino)phenylacetic acid;

3-Isobutyl-4-(3-(3-neo-pental-7-propyl-6-benz-[4,5]-isoxazoloxy)-propyloxy)phenylacetic acid;

3-Propyl-4-(3-(3-neo-pental-7-propyl-6-benz-[4,5]-isoxazoloxy)propylthio)phenylacetic acid S,S-dioxide;

-Chloro-4-(3-(3-phenyl-7-propyl-6-benz-[4,5]-isoxazoloxy)-propylsulfoxy)phenylacetic acid;

3-fluoro-4-(4-(3-phenyl-7-propyl-6-benz-[4, 5]-isoxazoloxy)-butyloxy)phenylacetic acid;

3-chloro-4-(3-(7-propyl-3-trifluoromethyl-6-benz-[4, 5]-isoxazoloxy)-propyl-thio)phenylacetic acid S, S-dioxide;

3-chloro-4-(3-(7-propyl-3-trifluoromethyl-6-benz-[4, 5]-isoxazoloxy)-propyl-thio)phenylacetic acid S-oxide;

- 20 -

3-chloro-4-(3-(2-phenylethyl)-7-propyl-6-benz[4,5]isoxazoloxy)propylthio)phenylacetic acid;

3-Chloro-4-(3-(3-(4-fluorophenyl)-7-propyl-6-benz-[4,5]-isoxazoloxy)-propylthio)phenylacetic acid;

3-Chloro-4-(3-(3-(4-fluorophenyl)-7-propyl-6-benz-[4,5]-isoxazoloxy)-propylsulfinyl)phenylacetic acid;

3-Chloro-4-(3-(3-(4-fluorophenyl)-7-propyl-6-benz-[4,5]-isoxazoloxy)-propylsulfonyl)) phenylacetic acid;

2,3-Dichloro-4-(3-(3-neo-pental-7-propyl-6-benz-[4,5]-isoxazoloxy)-propylthio)phenylacetic acid;

2-Trifluoroethoxy-4-(3-(3-neo-pental-7-propyl-6-benz-[4,5]-isoxazoloxy)propyloxy)phenylacetic acid;

3-Chloro-4-(3-(3-cyclopropyl)-7-propyl-6-benz-[4,5]-isoxazoloxy)-propylamino)phenylacetate;

2-(3-chloro-4-(3-(3-ethyl-7-propyl-6-benz-[4,5]-isoxazoloxy)propylthio)) phenylpropionic acid;

3-(4-(3-(3-phenyl-7-propyl-6-benz-[4,5]-isoxazoloxy)propyloxy)) phenylpropionic acid;

3-Chloro-4-(3-(3-(3-fluorophenyl)-7-propyl-6-benz-[4,5]-isoxazoloxy)-propylthio)phenylacetic acid;

3-Chloro-4-(3-(3-neo-pental-7-propyl-6-benz-[4,5]-isoxazoloxy)-propyloxy)phenoxyacetic acid;

4-(3-(3-phenyl-7-propyl-6-benz[4,5]isoxazole)oxy)propyloxy phenoxy acetic acid;

- 21 -

(3-(4-(3-phenyl-7-propyl-6-benz-[4,5]-isoxazoloxy)butyloxy))
phenylacetic acid;

3-(4-(4-(3-phenyl-7-propyl-6-benz-[4,5]-isoxazoloxy)butyloxy))
phenylpropionic acid;

3-chloro-4-(3-(2-methyl-2-phenylpropyl)-7-(n-propyl)-6-benz[4,5]isox-
azoloxy)propylthio)phenylacetic acid;

3-Methoxy-4-(3-(3-(2,2-dimethylpropyl)-7-propyl-6-benz-[4,5]-
isoxazoloxy)propyloxy)phenylacetate;

3-(4-(2-(3-phenyl-7-propyl-6-benz-[4,5]-isoxazoloxy)ethyloxy))
phenylpropionic acid;

(3-(4-(3-phenyl-7-propyl-6-benz-[4,5]-isoxazoloxy)butyloxy))
phenoxyacetic acid;

E-(4-(3-(3-phenyl-7-propyl-6-benz[4,5]isoxazole)oxy)propyloxy)
cinnamic acid;

E-(3-(3-(3-phenyl-7-propyl-6-benz[4,5]isoxazole)oxy)propyloxy)
cinnamic acid;

3-(3-(3-(3-phenyl-7-propyl-6-benz[4,5]isoxazole)oxy)propyloxy)
phenylpropionic acid;

N-((4-carbomethoxymethyl)benzoyl)-3(3-phenyl-7-propyl-6-benz-[4,7]-
isooxazolyloxy) propylamine ;

2-(4-(3-(3-phenyl-7-propyl-6-benz-[4,5]-isoxazoloxy)propyloxy))
phenoxypropionic acid;

2-(4-(4-(3-phenyl-7-propyl-6-benz-[4,5]-isoxazoloxy)butyloxy))
phenoxypropionic acid;

- 22 -

3-chloro-4-(3-(7-cyclopropylmethyl-3-phenyl-6-benz-[4, 5]-isoxazoloxy)propyl-thio)phenylacetic acid;

1-(3-chloro-4-(3-(3-(2,2-dimethylpropyl)-7-propyl-6-benz[4,5]isoxazole)oxy)propylthio) phenyl cyclopropane carboxylic acid;

4-(3-(3-(Ethyl)-7-(phenyl)-6-benz-[4,5]-isoxazoloxy)propyloxy)-3-chloro- α , α -dimethyl-phenyl propionic acid;

3-Ethoxy-4-(3-(3-(2,2-dimethylpropyl)-7-propyl-6-benz-[4,5]-isoxazoloxy)propyloxy)phenylacetate; and

3-chloro-4-(3-(3-phenyl-6-propyl-5-benz-[4,7]-isoxazolyloxy)-propylthio) phenylacetic acid.

Preferred examples of the compounds of the instant invention are:

Methyl 3-chloro-4-(3-(3-ethyl-7-propyl-6-benz-[4,5]-isoxazoloxy)-propylthio)phenylacetate;

3-chloro-4-(3-(3-ethyl-7-propyl-6-benz-[4,5]-isoxazoloxy)propylthio)-phenylacetic acid;

Methyl 3-chloro-4-(3-(3-methoxy-7-propyl-6-benz-[4,5]-isoxazoloxy)-propylthio)phenylacetate;

3-chloro-4-(3-(3-methoxy-7-propyl-6-benz-[4,5]-isoxazoloxy)propylthio)-phenylacetic acid;

Methyl 3-chloro-4-(3-(3-ethyl-7-propyl-6-benz-[4,5]-isothiazoloxy)-propylthio)phenyl acetate;

3-chloro-4-(3-(3-ethyl-7-propyl-6-benz-[4,5]-isothiazole)oxy)propylthio phenylacetic acid;

Methyl 3-chloro-4-(3-(3-methyl-7-propyl-6-benz-[4,5]-isoxazoloxy)-propylthio)phenylacetate;

3-chloro-4-(3-(3-methyl-7-propyl-6-benz-[4,5]-isoxazoloxy)propylthio)-phenylacetic acid;

Methyl 3-chloro-4-(3-(3,7-dipropyl-6-benz-[4,5]-isoxazoloxy)propylthio)-phenylacetate;

3-chloro-4-(3-(3,7-dipropyl-6-benz-[4,5]-isoxazoloxy)propylthio)phenyl-acetic acid;

Methyl 3-chloro-4-(3-(3-ethyl-7-propyl-6-benz-[4,5]-isoxazoloxy)-propylthio)phenylacetate S-oxide;

3-chloro-4-(3-(3-ethyl-7-propyl-6-benz-[4,5]-isoxazoloxy)propylthio)-phenylacetic acid S-oxide;

Methyl 3-chloro-4-(3-(3-ethyl-7-propyl-6-benz-[4,5]-isoxazoloxy)propyl-thio)phenylacetate S,S-dioxide;

3-Chloro-4-(3-(3-ethyl-7-propyl-6-benz-[4,5]-isoxazole)oxy)-propylthio phenylacetic acid S,S-dioxide;

tert-Butyl 3-chloro-4-(3-(3-ethyl-7-propyl-6-benz-[4,5]-isoxazoloxy)-propylthio)phenyl acetate;

2-methyl-2-(3-chloro-4-(3-(3-phenyl-7-propylbenz[4,5]isoxazol-6-oxy)propyl)thio)phenyl propionic acid;

Methyl 3-chloro-4-(3-(3-(2,2-dimethylpropyl)-7-propyl-6-benz-[4,5]-isoxazoloxy)-propylamino)phenylacetate;

- 24 -

3-Chloro-4-(3-(3-(2,2-dimethylpropyl)-7-propyl-6-benz-[4,5]-isoxazoloxy)-propylamino)phenylacetic acid;

3-Chloro-4-(3-(2-phenyl-6-propyl-5-benz-[4,7]-oxazoloxy)propylthio)phenylacetic acid;

Methyl 3-propyl-4-(3-(3-trifluoromethyl-7-propyl-6-benz-[4,5]-isoxazoloxy)-propylthio)phenylacetate;

3-propyl-4-(3-(3-trifluoromethyl-7-propyl-6-benz-[4,5]-isoxazoloxy)-propylthio)phenylacetic acid;

3-chloro-4-(3-(2-propyl-3-trifluoromethyl-6-benz-[4,5]-isoxazoloxy)propylthio)phenylacetic acid;

3-chloro-4-(3-(3-phenyl-7-cyclopropylmethyl-6-benz-[4,5]-isoxazoloxy)-butyloxy)phenylacetic acid;

4-(3-(3-Phenyl-7-propylbenzisoxazol-6-yloxy)propyloxy)-phenylacetic acid;

4-(3-(3-Phenyl-7-propylbenz[c]pyrazol-6-yloxy)propyloxy)-phenylacetic acid;

3-(4-(3-Phenyl-7-propylbenzisoxazol-6-yloxy)butyloxy)-phenylacetic acid;

3-(4-(3-Phenyl-7-propylbenz[c]pyrazol-6-yloxy)butyloxy)-phenylacetic acid;

4-(3-(3-Phenyl-7-propylbenzisoxazol-6-yloxy)propyloxy)-phenoxyacetic acid;

- 25 -

4-(3-(3-Phenyl-7-propylbenz[c]pyrazol-6-yloxy)propyloxy)-
phenoxyacetic acid;

4-(3-(3-Phenyl-7-propylbenzisoxazol-6-yloxy)propylthio)-3-
propylphenylacetic acid;

4-(4-(3-Phenyl-7-propylbenz[c]pyrazol-6-yloxy)butylthio)-3-
chlorophenylacetic acid;

4-(4-(1-Phenyl-4-propylbenz[c]pyrazol-5-yloxy)butylthio)-3-
chlorophenylacetic acid;

4-(3-(3-Phenyl-7-propylbenzisoxazol-6-yloxy)propylsulfonyl)-3-
propylphenylacetic acid;

4-(3-(3-Phenyl-7-propylbenz[c]pyrazol-6-yloxy)propylsulfonyl)-3-
chlorophenylacetic acid;

4-(4-(3-Phenyl-7-propylbenzisoxazol-6-yloxy)butylthio)-3-
propylbenzyl-tetrazole;

4-(4-(3-Phenyl-7-propylindol-6-yloxy)butylthio)-3-chlorobenzyl-
tetrazole;

4-(4-(1-Phenyl-4-propylindol-5-yloxy)butylthio)-3-chlorobenzyl-
tetrazole;

4-(3-(3-Phenyl-7-propylbenzisoxazol-6-yloxy)propylamino)-
phenylacetic acid;

4-(3-(3-Phenyl-7-propylbenz[c]pyrazol-6-yloxy)propylamino)-
phenylacetic acid;

- 26 -

3-(4-(4-(3-Phenyl-7-propylbenzisoxazol-6-yloxy)butyloxy)-phenylacetic acid;

3-(4-(4-(3-Phenyl-7-propylbenz[c]pyrazol-6-yloxy)butyloxy)-phenylacetic acid;

3-chloro-4-(3-(2,2-dimethylpropyl)-7-(n-propyl)-6-benz[4,5]isoxazoloxy)-propylthio)phenylacetic acid;

3-Propyl-4-(3-(3-ethyl-7-propyl-6-benz-[4,5]-isoxazoloxy)-propyloxy)phenylacetic acid;

4-(3-(3-(Ethyl)-7-propyl-6-benz-[4,5]-isoxazoloxy)butyl)phenylacetate;

3-chloro-4-(7-(n-propyl)-3-(3,3,3-trifluoropropyl)-6-benz[4,5]isoxazoloxy)propylthio)phenylacetic acid;

3-chloro-4-(3-(3-trifluoromethyl-7-propyl-6-benz-[4, 5]-isoxazoloxy)propylamino)phenylacetic acid;

-Chloro-4-(3-(3-phenyl-7-propyl-6-benz-[4,5]-isoxazoloxy)-propylsulfoxy)phenylacetic acid;

3-fluoro-4-(4-(3-phenyl-7-propyl-6-benz-[4, 5]-isoxazoloxy)-butyloxy)phenylacetic acid;

3-chloro-4-(3-(2-phenylethyl)-7-propyl-6-benz[4,5]isoxazoloxy)propylthio)phenylacetic acid;

3-Chloro-4-(3-(3-(4-fluorophenyl)-7-propyl-6-benz-[4,5]-isoxazoloxy)-propylthio)phenylacetic acid;

3-Chloro-4-(3-(3-(4-fluorophenyl)-7-propyl-6-benz-[4,5]-isoxazoloxy)-propylsulfonyl)) phenylacetic acid;

- 27 -

2,3-Dichloro-4-(3-(3-neo-pental-7-propyl-6-benz-[4,5]-isoxazoloxy)-propylthio)phenylacetic acid;

2-(3-chloro-4-(3-(3-ethyl-7-propyl-6-benz-[4,5]-isoxazoloxy)propylthio)) phenylpropionic acid;

3-(4-(3-(3-phenyl-7-propyl-6-benz-[4,5]-isoxazoloxy)propyloxy)) phenylpropionic acid;

3-Chloro-4-(3-(3-(3-fluorophenyl)-7-propyl-6-benz-[4,5]-isoxazoloxy)-propylthio)phenylacetic acid;

4-(3-(3-phenyl-7-propyl-6-benz[4,5]isoxazole)oxy)propyloxy phenoxy acetic acid;

(3-(4-(3-phenyl-7-propyl-6-benz-[4,5]-isoxazoloxy)butyloxy)) phenylacetic acid;

3-(4-(4-(3-phenyl-7-propyl-6-benz-[4,5]-isoxazoloxy)butyloxy)) phenylpropionic acid;

3-chloro-4-(3-(2-methyl-2-phenylpropyl)-7-(n-propyl)-6-benz[4,5]isoxazoloxy)propylthio)phenylacetic acid;

3-(4-(2-(3-phenyl-7-propyl-6-benz-[4,5]-isoxazoloxy)ethyloxy)) phenylpropionic acid;

(3-(4-(3-phenyl-7-propyl-6-benz-[4,5]-isoxazoloxy)butyloxy)) phenoxyacetic acid;

E-(4-(3-(3-phenyl-7-propyl-6-benz[4,5]isoxazole)oxy)propyloxy) cinnamic acid;

3-(3-(3-(3-phenyl-7-propyl-6-benz[4,5]isoxazole)oxy)propyloxy) phenylpropionic acid;

2-(4-(3-(3-phenyl-7-propyl-6-benz-[4,5]-isoxazoloxy)propyloxy)) phenoxypropionic acid;

- 28 -

2-(4-(4-(3-phenyl-7-propyl-6-benz-[4,5]-isoxazoloxy)butyloxy))
phenoxypropionic acid;

3-chloro-4-(3-(7-cyclopropylmethyl-3-phenyl-6-benz-[4, 5]-
isoxazoloxy)propyl-thio)phenylacetic acid;

1-(3-chloro-4-(3-(3-(2,2-dimethylpropyl)-7-propyl-6-
benz[4,5]isoxazole)oxy)propylthio) phenyl cyclopropane carboxylic
acid; and

4-(3-(3-(Ethyl)-7-(phenyl)-6-benz-[4,5]-isoxazoloxy)propyloxy)-3-
chloro- α , α -dimethyl-phenyl propionic acid.

The compounds of the present invention may have asymmetric centers and occur as racemates, racemic mixtures, and as individual diastereomers, with all possible isomers, including optical isomers, being included in the present invention.

Compounds of the general Formula I may be separated into diastereoisomeric pairs of enantiomers by, for example, fractional crystallization from a suitable solvent, for example methanol or ethyl acetate or a mixture thereof. The pair of enantiomers thus obtained may be separated into individual stereoisomers by conventional means, for example by the use of an optically active acid as a resolving agent.

Alternatively, any enantiomer of a compound of the general Formula I may be obtained by stereospecific synthesis using optically pure starting materials of known configuration.

The instant compounds can be isolated in the form of their pharmaceutically acceptable acid addition salts, such as the salts derived from using inorganic and organic acids. Examples of such acids are hydrochloric, nitric, sulfuric, phosphoric, formic, acetic, trifluoroacetic, propionic, maleic, succinic, malonic and the like. In addition, certain compounds containing an acidic function such as a carboxy or tetrazole, can be isolated in the form of their inorganic salt

- 29 -

in which the counterion can be selected from sodium, potassium, lithium, calcium, magnesium and the like, as well as from organic bases.

As previously indicated, the compounds of the present invention have valuable pharmacological properties. They are useful in treating or preventing diabetes, treating obesity, lowering triglyceride levels and prevention of vascular restenosis. They are useful in treating other disorders where insulin resistance is a component including ovarian hyperandrogenism (polycystic ovarian syndrome). They are also useful in raising high density lipoprotein levels, preventing, halting or slowing the progression of atherosclerotic cardiovascular diseases and related conditions and disease events.

The present invention also provides a compound of the general Formula I or a pharmaceutically acceptable salt thereof for use as an active therapeutic substance.

The present invention further provides a compound of the general Formula I, or a pharmaceutically acceptable ester thereof; or pharmaceutically acceptable salt thereof, for use in the treatment of hyperglycemia (diabetes) in human or non-human animals.

The present invention further provides a compound of the general Formula I, or a pharmaceutically acceptable ester thereof; or pharmaceutically acceptable salt thereof, in combination with known sulfonylureas, other insulin secretagogues as well as insulin for use in the treatment of diabetes treating obesity, lowering triglyceride levels, prevention of vascular restenosis, treating other disorders where insulin resistance is a component including ovarian hyperandrogenism (polycystic ovarian syndrome), raising high density lipoprotein levels, and preventing, halting or slowing the progression of atherosclerotic cardiovascular diseases and related conditions and disease events, and hypertension in human or non-human animals.

In one aspect, the present invention provides a compound of the general Formula I for use in the treatment of obesity in human or non-human animals. Said compound can be effectively used in combination with other known or proposed strategies for the treatment of obesity or obesity-related disorders; for example, fenfluramine,

- 30 -

dexfenfluramine, phentiramine and β_3 adrenergic receptor agonist agents.

The disease diabetes mellitus is characterized by metabolic defects in production and utilization of glucose which result in the failure to maintain appropriate blood sugar levels. The result of these defects is elevated blood glucose or hyperglycemia. Research on the treatment of diabetes has centered on attempts to normalize fasting and postprandial blood glucose levels. Treatments have included parenteral administration of exogenous insulin, oral administration of drugs and dietary therapies. The instant compounds can be effectively used in combination with known therapies for diabetes including insulin, sulfonylureas, biguanides (such as metformin), α -glucosidase inhibitors (such as acarbose) and others.

Two major forms of diabetes mellitus are now recognized. Type I diabetes, or insulin-dependent diabetes, is the result of an absolute deficiency of insulin, the hormone which regulates glucose utilization. Type II diabetes, or non-insulin-independent diabetes, often occurs in the face of normal, or even elevated levels of insulin and appears to be the result of the inability of tissues to respond appropriately to insulin. Most of the Type II diabetics are also obese. Accordingly, in another aspect the present invention provides a method of lowering triglyceride levels which comprises administering, to an animal in need thereof, a therapeutically effective amount of a compound of the formula I or pharmaceutically acceptable salt or ester thereof.

In addition the compounds of the present invention lower or modulate triglyceride levels and/or cholesterol levels and raise HDL plasma levels and are therefore of use in combating medical conditions wherein such lowering (and raising) is thought to be beneficial. Thus they may be used in the treatment of hypertension, obesity, atherosclerotic disease events, diabetes and related conditions by administering to an animal in need thereof, a therapeutically effective amount of a compound of the formula (I) or pharmaceutically acceptable salt thereof. The compositions are formulated and

- 31 -

administered in the same general manner as detailed below. They may also contain other active ingredients known for use in the treatment of atherosclerotic disease events, diabetes, hypertension, obesity and related conditions, for example fibrates such as clofibrate, bezafibrate and gemfibrozil; inhibitors of cholesterol biosynthesis such as HMG-CoA reductase inhibitors for example lovastatin, simvastatin and pravastatin; inhibitors of cholesterol absorption for example beta-sitosterol and (acyl CoA:cholesterol acyltransferase) inhibitors for example melinamide; anion exchange resins for example cholestyramine, colestipol or a dialkylaminoalkyl derivatives of a cross-linked dextran; nicotiny alcohol, nicotinic acid or a salt thereof; vitamin E; and thyromimetics.

In particular the invention provides methods for preventing or reducing the risk of developing atherosclerosis, comprising the administration of a prophylactically effective amount of a compound of formula I alone or in combination with one or more additional pharmaceutically active agents, to a mammal, particularly human, who is at risk of developing atherosclerosis.

Atherosclerosis encompasses vascular diseases and conditions that are recognized and understood by physicians practicing in the relevant fields of medicine. Atherosclerotic cardiovascular disease, coronary heart disease (also known as coronary artery disease or ischemic heart disease), cerebrovascular disease and peripheral vessel disease are all clinical manifestations of atherosclerosis and are therefore encompassed by the terms "atherosclerosis" and "atherosclerotic disease."

The instant invention further provides methods for preventing or reducing the risk of a first or subsequent (where the potential exists for recurrence) atherosclerotic disease event, comprising the administration of a prophylactically effective amount, or more particularly an HDL-raising amount, of a compound of formula I alone or in combination with one or more additional pharmaceutically active agents, to a mammal, particularly human, who is at risk for having an atherosclerotic disease event. The term "atherosclerotic disease event" as used herein is intended to encompass coronary heart disease events,

- 32 -

cerebrovascular events, and intermittent claudication. Coronary heart disease events are intended to include CHD death, myocardial infarction (i.e., a heart attack), and coronary revascularization procedures. Cerebrovascular events are intended to include ischemic or hemorrhagic stroke (also known as cerebrovascular accidents) and transient ischemic attacks. Intermittent claudication is a clinical manifestation of peripheral vessel disease. It is intended that persons who have previously experienced one or more non-fatal atherosclerotic disease event are those for whom the potential for recurrence of such an event exists.

Persons to be treated with the instant therapy include those at risk of developing atherosclerotic disease and of having an atherosclerotic disease event. Standard atherosclerotic disease risk factors are known to the average physician practicing in the relevant fields of medicine. Such known risk factors include but are not limited to hypertension, smoking, diabetes, low levels of high density lipoprotein cholesterol, high levels of low density lipoprotein cholesterol, and a family history of atherosclerotic cardiovascular disease. Published guidelines for determining those who are at risk of developing atherosclerotic disease can be found in: National Cholesterol Education Program, Second report of the Expert Panel on *Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel II)*, National Institute of Health, National Heart Lung and Blood Institute, NIH Publication No. 93-3095, September 1993; *abbreviated version*: Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults, *Summary of the second report of the national cholesterol education program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel II)*, *JAMA*, 1993, 269, pp. 3015-23. People identified as having one or more of the above-noted risk factors, as well as people who already have atherosclerosis, are intended to be included within the group of people considered to be at risk for having an atherosclerotic disease event.

- 33 -

The active compounds of the present invention may be orally administered as a pharmaceutical composition, for example, with an inert diluent, or with an assimilable edible carrier, or they may be enclosed in hard or soft shell capsules, or they may be compressed into tablets, or they may be incorporated directly with the food of the diet. For oral therapeutic administration, which includes sublingual administration, these active compounds may be incorporated with excipients and used in the form of tablets, pills, capsules, ampules, sachets, elixirs, suspensions, syrups, and the like. Such compositions and preparations should contain at least 0.1 percent of active compound. The percentage of active compound in these compositions may, of course, be varied and may conveniently be between about 2 percent to about 60 percent of the weight of the unit. The amount of active compound in such therapeutically useful compositions is such that an effective dosage will be obtained. The active compounds can also be administered intranasally as, for example, liquid drops or spray.

The effective dosage of active ingredient employed may vary depending on the particular compound employed, the mode of administration, the condition being treated and the severity of the condition being treated.

When treating or preventing diabetes mellitus and/or hyperglycemia or hypertriglyceridemia, or obesity, or when treating, preventing or slowing the progression of atherosclerosis generally satisfactory results are obtained when the compounds of the present invention are administered at a daily dosage of from about 0.1 milligram to about 100 milligram per kilogram of animal body weight, preferably given as a single daily dose or in divided doses two to six times a day, or in sustained release form. For most large mammals, the total daily dosage is from about 1.0 milligrams to about 1000 milligrams, preferably from about 1 milligrams to about 50 milligrams. In the case of a 70 kg adult human, the total daily dose will generally be from about 7 milligrams to about 350 milligrams. This dosage regimen may be adjusted to provide the optimal therapeutic response.

- 34 -

The compositions are formulated and administered in the same general manner as detailed below. The compounds of the instant invention may be used effectively alone or in combination with one or more additional active agents depending on the desired target therapy. Combination therapy includes administration of a single pharmaceutical dosage formulation which contains a compound of formula I and one or more additional active agents, as well as administration of a compound of formula I and each active agent in its own separate pharmaceutical dosage formulation. For example, a compound of formula I and an HMG-CoA reductase inhibitor can be administered to the patient together in a single oral dosage composition such as a tablet or capsule, or each agent administered in separate oral dosage formulations. Where separate dosage formulations are used, a compound of formula I and one or more additional active agents can be administered at essentially the same time, i.e., concurrently, or at separately staggered times, i.e., sequentially; combination therapy is understood to include all these regimens.

An example of combination treatment or prevention of atherosclerosis may be wherein a compound of formula I is administered in combination with one or more of the following active agents: *an antihyperlipidemic agent; a plasma HDL-raising agent; an antihypercholesterolemic agent such as a cholesterol biosynthesis inhibitor, for example an HMG-CoA reductase inhibitor, an HMG-CoA synthase inhibitor, a squalene epoxidase inhibitor, or a squalene synthetase inhibitor (also known as squalene synthase inhibitor); an acyl-coenzyme A: cholesterol acyltransferase (ACAT) inhibitor such as melinamide; probucol; nicotinic acid and the salts thereof and niacinamide; a cholesterol absorption inhibitor such as beta-sitosterol; a bile acid sequestrant anion exchange resin such as cholestyramine, colestipol or dialkylaminoalkyl derivatives of a cross-linked dextran; an LDL (low density lipoprotein) receptor inducer; fibrates such as clofibrate, bezafibrate, fenofibrate, and gemfibrozil; vitamin B6 (also known as pyridoxine) and the pharmaceutically acceptable salts thereof*

- 35 -

such as the HCl salt; vitamin B₁₂ (also known as cyanocobalamin); antioxidant vitamins such as vitamin C and E and beta carotene; a beta-blocker; an angiotensin II antagonist; an angiotensin converting enzyme inhibitor; and a platelet aggregation inhibitor such as fibrinogen receptor antagonists (i.e., glycoprotein IIb/IIIa fibrinogen receptor antagonists) and aspirin. As noted above, the compounds of formula I can be administered in combination with more than one additional active agent, for example, a combination of a compound of formula I with an HMG-CoA reductase inhibitor (e.g. lovastatin, simvastatin and pravastatin) and aspirin, or a compound of formula I with an HMG-CoA reductase inhibitor and a beta blocker.

Another example of combination therapy can be seen in treating obesity or obesity-related disorders, wherein the compounds of formula I may be effectively used in combination with for example, fenfluramine; dexfenfluramine, phentiramine and β_3 adrenergic receptor agonist agents.

Still another example of combination therapy can be seen in treating diabetes and related disorders wherein the compounds of formula I can be effectively used in combination with for example sulfonylureas, biguanides, α -glucosidase inhibitors, other insulin secretagogues, insulin as well as the active agents discussed above for treating atherosclerosis.

In accordance with this invention, a pharmaceutically effective amount of a compound of formula I can be used for the preparation of a medicament useful for treating diabetes, treating obesity, lowering tryglyeride levels, raising the plasma level of high density lipoprotein, and for treating, preventing or reducing the risk of developing atherosclerosis, and for preventing or reducing the risk of having a first or subsequent atherosclerotic disease event in mammals, particularly in humans.

Additionally, an effective amount of a compound of formula I and a therapeutically effective amount of one or more active agents selected from the group consisting of: *an antihyperlipidemic agent; a plasma HDL-raising agent; an antihypercholesterolemic agent*

- 36 -

such as a cholesterol biosynthesis inhibitor, for example an HMG-CoA reductase inhibitor, *an HMG-CoA synthase inhibitor, a squalene epoxidase inhibitor, or a squalene synthetase inhibitor (also known as squalene synthase inhibitor)*; an acyl-coenzyme A: cholesterol acyltransferase inhibitor; probucol; nicotinic acid and the salts thereof; niacinamide; a cholesterol absorption inhibitor; a bile acid sequestrant anion exchange resin; a low density lipoprotein receptor inducer; clofibrate, fenofibrate, and gemfibrozol; vitamin B₆ and the pharmaceutically acceptable salts thereof; vitamin B₁₂; an anti-oxidant vitamin; a beta-blocker; an angiotensin II antagonist; an angiotensin converting enzyme inhibitor; a platelet aggregation inhibitor; a fibrinogen receptor antagonist; aspirin; fenfluramines, dexfenfluramines, phentiramines, β_3 adrenergic receptor agonists; sulfonylureas, biguanides, α -glucosidase inhibitors, other insulin secretagogues, and insulin can be used together for the preparation of a medicament useful for the above-described treatments.

The tablets, pills, capsules, and the like may also contain a binder such as gum tragacanth, acacia, corn starch or gelatin; excipients such as dicalcium phosphate; a disintegrating agent such as corn starch, potato starch, alginic acid; a lubricant such as magnesium stearate; and a sweetening agent such as sucrose, lactose or saccharin. When a dosage unit form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier such as a fatty oil.

Various other materials may be present as coatings or to modify the physical form of the dosage unit. For instance, tablets may be coated with shellac, sugar or both. A syrup or elixir may contain, in addition to the active ingredient, sucrose as a sweetening agent, methyl and propylparabens as preservatives, a dye and a flavoring such as cherry or orange flavor.

These active compounds may also be administered parenterally. Solutions or suspensions of these active compounds can be prepared in water suitably mixed with a surfactant such as hydroxypropylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols and mixtures thereof in oils. Under ordinary

- 37 -

conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

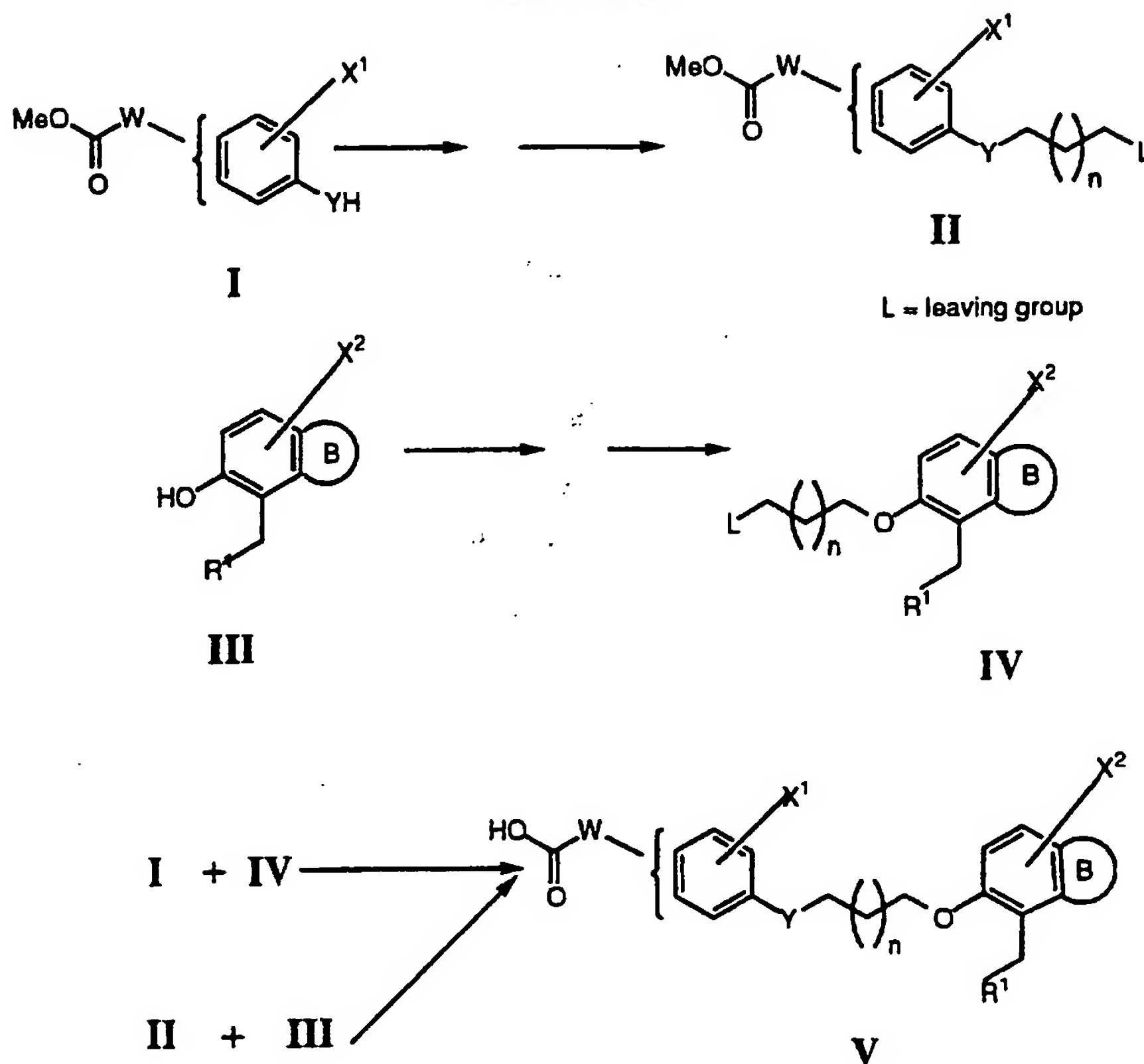
The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases, the form must be sterile and must be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (e.g. glycerol, propylene glycol and liquid polyethylene glycol), suitable mixtures thereof, and vegetable oils.

Specific examples of formula I may require the use of protecting groups to enable their successful elaboration into the desired structure. Protecting groups may be chosen with reference to Greene, T.W., et al., Protective Groups in Organic Synthesis, John Wiley & Sons, Inc., 1991. The blocking groups are readily removable, i.e., they can be removed, if desired, by procedures which will not cause cleavage or other disruption of the remaining portions of the molecule. Such procedures include chemical and enzymatic hydrolysis, treatment with chemical reducing or oxidizing agents under mild conditions, treatment with fluoride ion, treatment with a transition metal catalyst and a nucleophile, and catalytic hydrogenation.

Examples of suitable hydroxyl protecting groups are: trimethylsilyl, triethylsilyl, o-nitrobenzyloxycarbonyl, p-nitrobenzyloxycarbonyl, t-butyldiphenylsilyl, t-butyldimethylsilyl, benzyloxycarbonyl, t-butyloxycarbonyl, 2,2,2-trichloroethyloxycarbonyl, and allyloxycarbonyl. Examples of suitable carboxyl protecting groups are benzhydryl, o-nitrobenzyl, p-nitrobenzyl, 2-naphthylmethyl, allyl, 2-chloroallyl, benzyl, 2,2,2-trichloroethyl, trimethylsilyl, t-butyldimethylsilyl, t-butldiphenylsilyl, 2-(trimethylsilyl)ethyl, phenacyl, p-methoxybenzyl, acetonyl, p-methoxyphenyl, 4-pyridylmethyl and t-butyl.

- 38 -

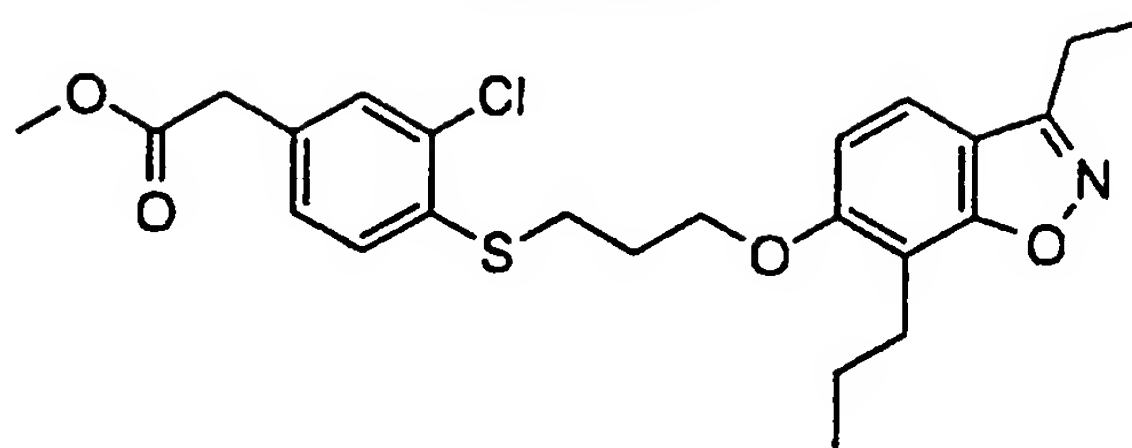
The process for making the compounds of the instant invention is generally depicted in Scheme 1 below:

SCHEME 1

L is a leaving group such as halo, preferably bromide, or sulfonyloxy, preferably mesyloxy or tosyloxy.

The following examples are provided so that the invention might be more fully understood. They should not be construed as limiting the invention in any way.

- 39 -

Example 1

Methyl 3-chloro-4-(3-(3-ethyl-7-propyl-6-benz-[4,5]-isoxazoloxy)-propylthio)phenylacetate

Step A: Preparation of 1-bromo-3-(2-hydroxy-3-propyl-4-propionyl)-phenoxy)propane

A solution of 2,4-dihydroxy-3-propylphenyl ethyl ketone (25.545 grams) in 2-butanone (300 mL) was treated with 1,3-dibromopropane (48.79 mL) and potassium carbonate (50.859 grams). The mixture was refluxed for 4 hours. The reaction mixture was partitioned between isopropyl acetate and pH 4 buffer. The organic was washed once with water, then dried over magnesium sulfate. The organic was filtered and evaporated to an oil which was chromatographed over silica gel with hexane/methylene chloride (2:1) to afford the title compound.

NMR (CDCl₃) δ 7.62 (d, 1H, J = 8.8 Hz), 6.43 (d, 1H, J = 8.8 Hz), 4.16 (t, 2H, J = 5.8 Hz), 3.60 (t, 2H, J = 6.4 Hz), 2.94 (quart, 2H, J = 7.3 Hz), 2.61 (bt, 2H, J = 7.5 Hz).

Step B: Preparation of methyl 3-chloro-4-(3-(2-propyl-3-hydroxy-4-propionylphenoxy)propylthio)phenylacetate

A solution of 3-chloro-4-dimethylcarbamoylthio-phenylacetic acid methyl ester (33.038 grams) in dry methanol (350 mL) was treated with a solution of sodium methoxide in methanol (25wt%; 34.15 mL). The solution was refluxed for 2 hours. HPLC analysis showed the disappearance of the carbamate. The solution was allowed to cool to 50°C. 1-bromo-3-(2-hydroxy-3-propyl-4-

- 40 -

propionyl)-phenoxy)propane (Step A; 31.500 grams) was added and the solution stirred for 1 hour. The reaction was partitioned between isopropyl acetate and pH 4 buffer. The organic was washed once more with pH 4 buffer, then water. The organic was dried over magnesium sulfate, filtered and concentrated to an oil. The oil was applied to a silica gel column packed with hexane/methylene chloride (2:1). The column was eluted with this mobile phase until the product began to appear in the eluant. The mobile phase was switched to 100% methylene chloride and elution continued until all the title compound was recovered.

NMR (Acetone) δ 7.81 (d, 1H, $J = 9.1$ Hz), 7.25 (dd, 1H, $J = 8.1, 1.8$ Hz), 6.62 (d, 1H, $J = 9.1$ Hz), 4.27 (t, 2H, $J = 5.9$ Hz), 3.64 (s, 3H), 3.25 (t, 2H, $J = 7.5$ Hz), 3.04 (quart, 2H, $J = 7.3$ Hz), 2.65 (bt, 2H, $J = 7.6$ Hz).

Step C: Preparation of methyl 3-chloro-4-(3-(2-propyl-3-hydroxy-4-(1-hydroxyiminopropyl)phenoxy)propylthio)-phenylacetate

A solution of methyl 3-chloro-4-(3-(2-propyl-3-hydroxy-4-propionylphenoxy)propylthio)phenylacetate (Step B; 25.655 grams) in dry methanol (260 mL) was treated with hydroxylamine hydrochloride (3.833 grams). Anhydrous sodium acetate (4.524 grams) was added and the mixture refluxed for 4 hours. The reaction mixture was partitioned between isopropyl acetate and pH 7 buffer. The organic phase was washed once with water and dried over magnesium sulfate, filtered and evaporated to an oil. The title compound was used without further purification.

NMR (CDCl₃) δ 7.11 (dd, 1H, $J = 8.1, 1.8$ Hz), 6.42 (d, 1H, $J = 8.9$ Hz), 4.09 (t, 2H, $J = 5.7$ Hz), 3.68 (s, 3H), 3.14 (t, 2H, $J = 7.2$ Hz), 2.83 (quart, 2H, $J = 7.7$ Hz), 2.66 (bt, 2H, $J = 7.7$ Hz).

Step D: Preparation of methyl 3-chloro-4-(3-(2-propyl-3-hydroxy-4-(1-acetoxyiminopropyl)phenoxy)propylthio)phenylacetate

- 41 -

A solution of methyl 3-chloro-4-(3-(2-propyl-3-hydroxy-4-(1-hydroxyiminopropyl)phenoxy)propylthio)phenyl acetate (Step C; 5.96 grams) in acetic anhydride (50 mL) was stirred for 16 hours. The solvent was removed *in vacuo*. The remaining residue was dissolved in isopropyl acetate and washed with pH 7 buffer. The organic phase was dried over magnesium sulfate, filtered and evaporated. The title compound was used without further purification.

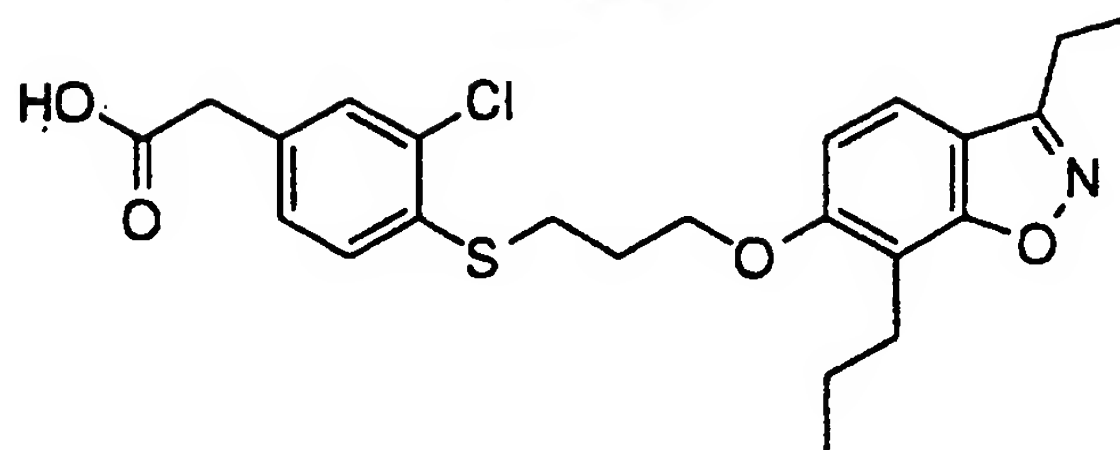
NMR (CDCl₃) δ 7.11 (dd, 1H, J = 8.0, 1.9 Hz), 6.44 (d, 1H, J = 8.8 Hz), 4.10 (t, 2H, J = 5.7 Hz), 3.68 (s, 3H), 3.13 (t, 2H, J = 7.2 Hz), 2.86 (quart, 2H, J = 7.6 Hz), 2.67 (bt, 2H, J = 7.6 Hz), 2.22 (s, 3H).

Step E: Preparation of methyl 3-chloro-4-(3-(3-ethyl-7-propyl-6-benz-[4,5]-isoxazoloxy)propylthio)phenylacetate

A solution of methyl 3-chloro-4-(3-(2-propyl-3-hydroxy-4-(1-acetoxyiminopropyl)phenoxy)propylthio)phenylacetate (Step D; 6.19 grams) in dry pyridine (65 mL) was refluxed for 3 hours. The solvent was removed *in vacuo* and the residue partitioned between isopropyl acetate and 0.1N HCl. The organic was washed once more with 0.1N HCl. The organic was dried over magnesium sulfate, filtered and evaporated to an oil. The crude product was placed on a silica gel column and eluted with hexane/CH₂Cl₂ (1:1) until the product appeared in the eluant. The mobile phase was changed to 100% CH₂Cl₂ and elution continued until all the title compound was recovered.

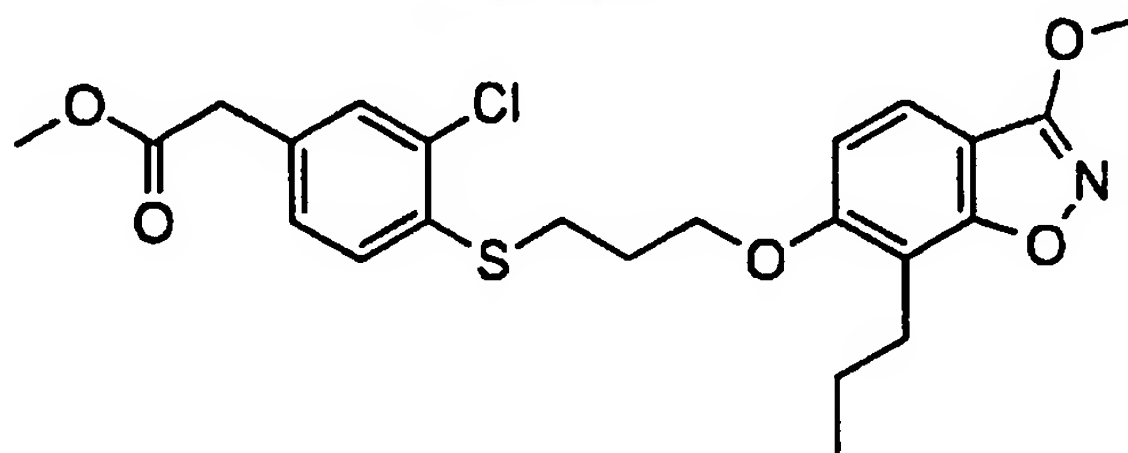
NMR (CDCl₃) δ 7.38 (d, 1H, J = 8.6 Hz), 7.10 (dd, 1H, J = 8.1, 1.8 Hz), 6.87 (d, 1H, J = 8.6 Hz), 4.17 (t, 2H, J = 5.8 Hz), 3.68 (s, 3H), 3.16 (t, 2H, J = 7.1 Hz), 2.94 (quart, 2H, J = 7.6 Hz), 2.85 (bt, 2H, J = 7.5 Hz).

- 42 -

Example 23-chloro-4-(3-(3-ethyl-7-propyl-6-benz-[4,5]-isoxazoloxy)propylthio)-phenylacetic acid

A solution of methyl 3-chloro-4-(3-(3-ethyl-7-propyl-6-benz-[4,5]-isoxazoloxy)propylthio)phenylacetate (4.95 grams) in methanol (95 mL) was treated with a solution of LiOH in water (1.299 M; 16.50 mL). The solution was refluxed for 1 hour. The solution was partitioned between isopropyl acetate and 0.1N HCl. The organic layer was dried over magnesium sulfate, filtered and evaporated to a solid. The solid was suspended in methylene chloride (18 mL) and heated to reflux. Cyclohexane (18mL) was added dropwise while refluxing. The solution was cooled to 0°C and the title compound isolated by filtration.

NMR (CDCl₃) δ 7.38 (d, 1H, J = 8.7 Hz), 7.10 (dd, 1H, J = 8.1, 1.8 Hz), 6.87 (d, 1H, J = 8.7 Hz), 4.17 (t, 2H, J = 5.8 Hz), 3.57 (s, 2H), 3.16 (t, 2H, J = 7.1 Hz), 2.94 (quart, 2H, J = 7.6 Hz), 2.85 (bt, 2H, J = 7.5 Hz).

Example 3Methyl 3-chloro-4-(3-(3-methoxy-7-propyl-6-benz-[4,5]-isoxazoloxy)-propylthio)phenylacetate

- 43 -

Step A: Preparation of methyl 2-hydroxy-3-propyl-4-benzyloxy-benzoate

A solution of methyl 2,4-dihydroxy-3-propylbenzoate (3.00 grams) in 2-butanone (30 mL) was treated with benzyl bromide (1.70 mL) and potassium carbonate (1.972 grams). The mixture was refluxed for 4 hours. The reaction mixture was partitioned between isopropyl acetate and pH 4 buffer. The organic was washed once with water, then dried over magnesium sulfate. The organic was filtered and evaporated to an oil which was chromatographed over silica gel to afford the title compound.

NMR (CDCl₃) δ 7.67 (d, 1H, J = 8.9 Hz), 7.42-7.29 (m, 5H), 6.48 (d, 1H, J = 8.9 Hz), 5.12 (bs, 2H), 3.89 (s, 3H), 2.69 (bt, 2H, J = 7.4 Hz).

Step B: Preparation of 2-hydroxy-3-propyl-4-benzyloxyphenyl hydroxamic acid

A solution of methyl 2-hydroxy-3-propyl-4-benzyloxy benzoate (Step A; 0.863 grams) in dry methanol (8 mL) was treated with hydroxylamine hydrochloride (0.299 grams) and a solution of methanolic sodium methoxide (25 wt%; 0.986 mL). The solution was refluxed for 8 hours. The reaction was partitioned between isopropyl acetate and pH 4 buffer. The organic was dried over magnesium sulfate, filtered and concentrated to a solid. The title compound was used without further purification.

NMR (CD₃OD) δ 7.45-7.26 (m, 6H), 6.54 (d, 1H, J = 8.8 Hz), 5.12 (bs, 2H), 2.67 (bt, 2H, J = 7.4 Hz).

Step C: Preparation of 3-hydroxy-6-benzyloxy-7-propylbenz-[4,5]-isoxazole

A solution of 2-hydroxy-3-propyl-4-benzyloxyphenyl hydroxamic acid (Step B; 0.477 grams) in dry THF (5 mL) was treated with carbonyl di-imidazole (0.513 grams). The solution was stirred at 50° for 14 hours. The reaction was partitioned between isopropyl acetate and pH 4 buffer. The organic was dried over magnesium sulfate, filtered and evaporated to a solid which was digested in

- 44 -

refluxing *tert*-butyl methyl ether. The mixture was allowed to cool to 25°C and the product recovered by filtration. The title compound was used without further purification.

NMR (CD₃OD) δ 7.89 (d, 1H, J = 8.8 Hz), 7.47-7.31 (m, 5H), 7.18 (d, 1H, J = 8.8 Hz), 5.25 (bs, 2H), 2.80 (bt, 2H, J = 7.4 Hz).

Step D: Preparation of 3-methoxy-6-benzyloxy-7-propylbenz-[4,5]-isoxazole

A solution of 3-hydroxy-6-benzyloxy-7-propylbenz-[4,5]-isoxazole (Step C; 195 mg) in acetone (3 mL) was treated with methyl iodide (0.067 mL) and potassium carbonate (100 mg). The mixture was refluxed for 8 hours. The reaction was partitioned between isopropyl acetate and pH 4 buffer. The organic was dried over magnesium sulfate, filtered and concentrated to a solid, which was chromatographed over silica gel to afford the title compound.

NMR (CD₃OD) δ 7.89 (vbd, 1H, J = 8.8 Hz), 7.47-7.31 (m, 5H), 7.16 (vbd, 1H, J = 8.8 Hz), 5.23 (bs, 2H), 3.97 (s, 3H), 2.79 (vbt, J = 7.3 Hz).

Step E: Preparation of 3-methoxy-6-hydroxy-7-propylbenz-[4,5]-isoxazole

A solution of 3-methoxy-6-benzyloxy-7-propylbenz-(4,5)-isoxazole (Step E; 181 mg) in ethyl acetate (4 mL) was treated with 10% palladium on carbon catalyst (25 mg). The mixture was shaken under a hydrogen atmosphere (40 psi) for 3 hours. The mixture was filtered through Celite and concentrated to a solid. The title compound was used without further purification.

NMR (CD₃OD) δ 7.70 (d, 1H, J = 8.9 Hz), 6.80 (d, 1H, J = 8.9 Hz), 3.93 (s, 3H), 2.69 (bt, 2H, J = 7.6 Hz).

Step F: Preparation of 3-methoxy-6-(3-bromopropyl)oxy-7-propyl-benz-[4,5]-isoxazole

Using the method of Example 1, Step A, substituting 3-methoxy-6-hydroxy-7-propylbenz-(4,5)-isoxazole (Step E) as the starting material, the title compound was obtained.

- 45 -

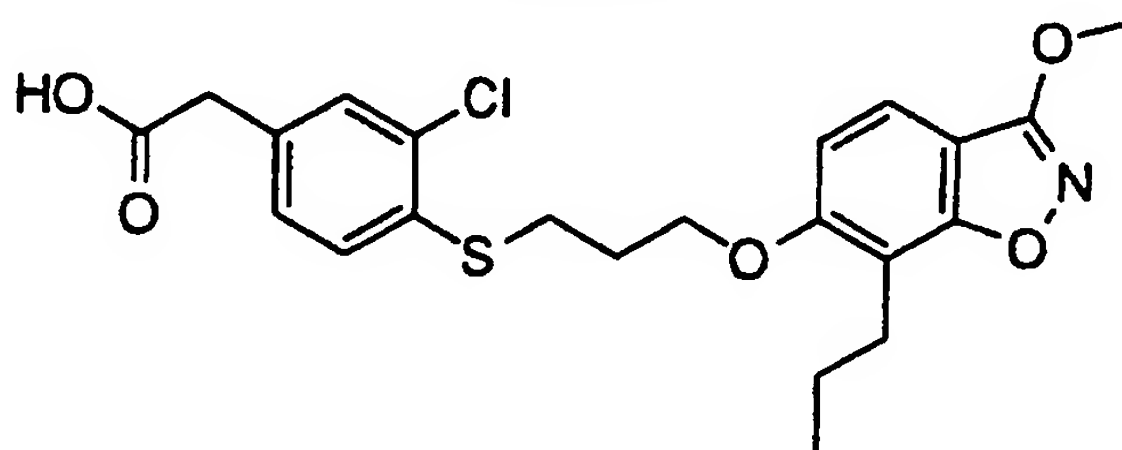
NMR (CDCl₃) δ 7.92 (d, 1H, J = 8.9 Hz), 6.90 (d, 1H, J = 8.8 Hz), 4.22 (t, 2H, J = 5.8 Hz), 4.04 (s, 3H), 3.60 (t, 2H, J = 6.3 Hz), 2.72 (bt, 2H, J = 7.5 Hz).

Step G: Preparation of methyl 3-chloro-4-(3-(3-methoxy-7-propyl-6-benz-[4,5]-isoxazoloxy)propylthio)phenylacetate

Using the method of Example 1, Step B, substituting 3-methoxy-6-(3-bromopropyl)oxy-7-propyl-benz-[4,5]-isoxazole as the starting material, the title compound was obtained.

NMR (CDCl₃) δ 7.66 (d, 1H, J = 8.9 Hz), 7.10 (dd, 1H, J = 8.1, 1.8 Hz), 6.40 (d, 1H, J = 8.9 Hz), 4.14 (t, 2H, J = 5.7 Hz), 3.89 (s, 3H), 3.68 (s, 3H), 3.13 (t, 2H, J = 7.2 Hz), 2.65 (bt, 2H, J = 7.6 Hz).

Example 4



3-chloro-4-(3-(3-methoxy-7-propyl-6-benz-[4,5]-isoxazoloxy)-propylthio)-phenylacetic acid

1. 2-hydroxy-3-propyl-4-benzyloxyphenyl hydroxamic acid

A solution of 2-hydroxy-3-propyl-4-benzyloxy benzoic acid methyl ester (0.863 grams) in dry methanol (8 mL) was treated with hydroxylamine hydrochloride (0.299 grams) and a solution of methanolic sodium methoxide (25 wt%; 0.986 mL). The solution was refluxed for 8 hours. The reaction was partitioned between isopropyl acetate and pH 4 buffer. The organic was dried over magnesium sulfate, filtered and concentrated to a solid. The product was used without further purification.

NMR (CD₃OD) δ 7.45-7.26 (m, 6H), 6.54 (d, 1H, J = 8.8 Hz), 5.12 (bs, 2H), 2.67 (bt, 2H, J = 7.4 Hz).

- 46 -

2. 3-hydroxy-6-benzyloxy-7-propyl-benz[4,5]isoxazole

A solution of 2-hydroxy-3-propyl-4-benzyloxyphenyl hydroxamic acid (0.477 grams) in dry THF (5 mL) was treated with carbonyl di-imidazole (0.513 grams). The solution was stirred at 50° for 14 hours. The reaction was partitioned between isopropyl acetate and pH 4 buffer. The organic was dried over magnesium sulfate, filtered and evaporated to a solid which was digested in refluxing *tert*-butyl methyl ether. The mixture was allowed to cool to 25°C and the product recovered by filtration. The product was used without further purification.

NMR (CD₃OD) δ 7.89 (d, 1H, J = 8.8 Hz), 7.47-7.31 (m, 5H), 7.18 (d, 1H, J = 8.8 Hz), 5.25 (bs, 2H), 2.80 (bt, 2H, J = 7.4 Hz).

3. 3-methoxy-6-benzyloxy-7-propyl-benz[4,5]isoxazole

A solution of 3-hydroxy-6-benzyloxy-7-propyl benz[4,5]isoxazole (195 mg) in acetone (3 mL) was treated with methyl iodide (0.067 mL) and potassium carbonate (100 mg). The mixture was refluxed for 8 hours. The reaction was partitioned between isopropyl acetate and pH 4 buffer. The organic was dried over magnesium sulfate, filtered and concentrated to a solid, which was chromatographed over silica gel to afford the product.

NMR (CD₃OD) δ 7.89 (vbd, 1H, J = 8.8 Hz), 7.47-7.31 (m, 5H), 7.16 (vbd, 1H, J = 8.8 Hz), 5.23 (bs, 2H), 3.97 (s, 3H), 2.79 (vbt, J = 7.3 Hz).

4. 3-methoxy-6-hydroxy-7-propyl-benz[4,5]isoxazole

A solution of 3-methoxy-6-benzyloxy-7-propyl benz-(4,5)-isoxazole (181 mg) in ethyl acetate (4 mL) was treated with 10% palladium on carbon catalyst (25 mg). The mixture was shaken under a hydrogen atmosphere (40 psi) for 3 hours. The mixture was filtered through Celite and concentrated to a solid. The product was used without further purification.

NMR (CD₃OD) δ 7.70 (d, 1H, J = 8.9 Hz), 6.80 (d, 1H, J = 8.9 Hz), 3.93 (s, 3H), 2.69 (bt, 2H, J = 7.6 Hz).

- 47 -

5. 1-bromo-3-(3-methoxy-7-propyl-6-benz[4,5]isoxazole)oxy propane

A solution of 3-methoxy-6-hydroxy-7-propyl-benz[4,5]isoxazole (0.112 grams) in 2-butanone (1.5 mL) was treated with 1,3-dibromopropane (0.215 mL) and potassium carbonate (0.078 grams). The mixture was stirred at 60°C for 16 hours. The reaction was partitioned between isopropyl acetate and pH 4 phosphate buffer. The organic was dried over magnesium sulfate, filtered and evaporated to a residue. The product was purified by silica gel chromatography. NMR (CDCl₃) δ 7.92 (d, 1H, J = 8.9 Hz), 6.90 (d, 1H, J = 8.9 Hz), 4.12 (t, 2H, J = 5.6 Hz), 4.03 (s, 3H), 3.60 (t, 2H, J = 6.5 Hz), 2.72 (bt, 2H, J = 7.5 Hz).

6. Methyl 3-chloro-4-(3-(3-methoxy-7-propyl-6-benz[4,5]isoxazole)oxy)propylthio phenyl acetate

A solution of 3-chloro-4-dimethylcarbamoylthiophenyl acetic acid methyl ester (0.109 grams; 0.380 mmol) in dry methanol (2 mL) was treated with a solution of sodium methoxide in methanol (25wt%; 0.122 mL). The solution was refluxed for 2 hours. LC analysis showed the disappearance of the carbamate. The solution was allowed to cool to ambient temperature. 1-bromo-3-(3-methoxy-7-propyl-6-benz[4,5]isoxazole)oxy propane (0.104 grams; 0.317 mmol) was added and the solution stirred for 1 hour. The reaction was partitioned between isopropyl acetate and pH 4 buffer. The organic was dried over magnesium sulfate, filtered and concentrated to an oil. The oil was chromatographed over silica gel to afford the title compound. NMR (CDCl₃): 7.66 (d, 1H, J = 8.9 Hz); 7.11 (dd, 1H, J = 8.1, 1.9 Hz); 6.39 (d, 1H, J = 8.9 Hz); 4.12 (t, 2H, J = 5.7 Hz); 3.89 (s, 3H); 3.68 (s, 3H); 3.58 (s, 2H); 3.13 (t, 2H, J = 7.1 Hz); 2.63 (bt, 2H, J = 7.6 Hz).

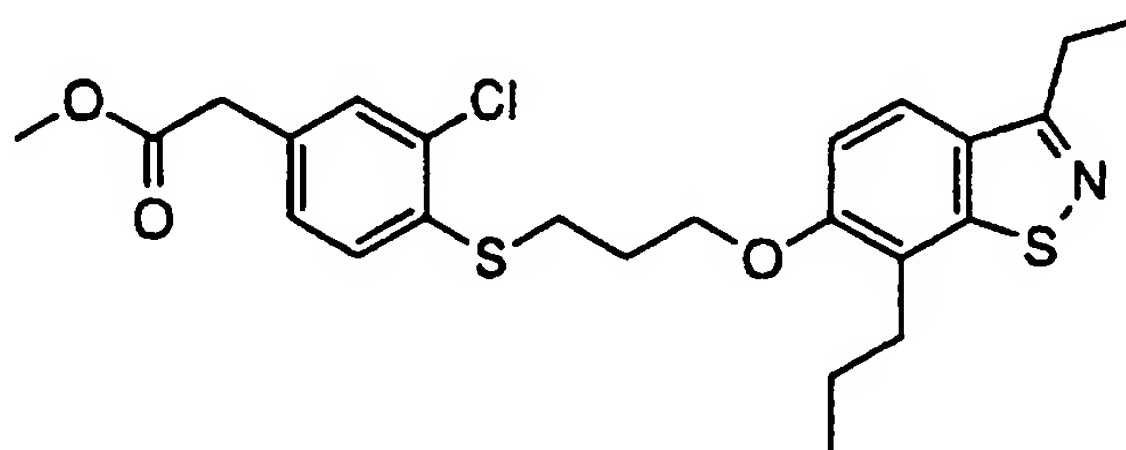
7. 3-chloro-4-(3-(3-methoxy-7-propyl-6-benz[4,5]isoxazole)oxy)propylthio phenyl acetic acid

- 48 -

A solution of methyl 3-chloro-4-(3-(3-methoxy-7-propyl-6-benz[4,5]isoxazole)oxy)propylthio phenyl acetate (0.130 grams; 0.280 mmol) in methanol (2 mL) was treated with a solution of LiOH in water (1.084 M; 0.387 mL). The solution was refluxed for 1 hour. The solution was partitioned between isopropyl acetate and 0.1N HCl. The organic layer was dried over magnesium sulfate, filtered and evaporated to a solid. The solid was suspended in methylene chloride (1 mL) and heated to reflux. Cyclohexane (2 mL) was added dropwise while refluxing. The solution was cooled to 0°C and the product isolated by filtration.

NMR (CDCl₃): 7.66 (d, 1H, J = 8.9 Hz), 7.11 (dd, 1H, J = 8.1, 1.9 Hz), 6.39 (d, 1H, J = 8.9 Hz), 4.12 (t, 2H, J = 5.7 Hz), 3.89 (s, 3H), 3.58 (s, 2H), 3.13 (t, 2H, J = 7.1 Hz), 2.63 (bt, 2H, J = 7.6 Hz).

Example 5



Methyl 3-chloro-4-(3-(3-ethyl-7-propyl-6-benz-[4,5]-isothiazoloxy)-propylthio)phenyl acetate

Step A: Preparation of 2-chloro-3-(3-propenyl)-4-hydroxy-benzaldehyde

A solution of 2-chloro-4-(3-propenyl)oxybenzaldehyde (6.62 grams) in ortho-dichlorobenzene (40 mL) was refluxed for 22 hours. The solvent was removed *in vacuo* and the derived solid was chromatographed over silica gel to afford the title compound.

- 49 -

NMR (CD₃OD) δ 10.28 (s, 1H), 7.79 (d, 1H, J = 8.9 Hz), 6.84 (d, 1H, J = 8.9 Hz), 5.90 (m, 1H), 5.03-4.95 (two overlapping dd, 2H), 3.68 (d, 2H, J = 4.7 Hz).

Step B: Preparation of 2-chloro-3-propyl-4-hydroxybenzaldehyde

A solution of 2-chloro-3-(3-propenyl)-4-hydroxybenzaldehyde (Step A; 0.923 grams) in methyl *tert*-butyl ether (10 mL) was treated with 5% rhodium on alumina (140 mg). The mixture was shaken under a hydrogen atmosphere (21 psi) for 2 hours. The mixture was filtered through Celite and evaporated to a solid. The title compound was used without further purification.

NMR (CD₃OD) δ 10.27 (s, 1H), 7.64 (d, 1H, J = 8.8 Hz), 6.81 (d, 1H, J = 8.7 Hz), 2.79 (bt, 2H, J = 7.6 Hz).

Step C: Preparation of 2-chloro-3-propyl-4-benzyloxybenzaldehyde

Using the method of Example 3, Step A, substituting 2-chloro-3-(3-propenyl)-4-hydroxybenzaldehyde (Step B) as the starting material, the title compound was obtained.

NMR (acetone) δ 10.35 (s, 1H), 7.79 (d, 1H, J = 8.8 Hz), 7.22 (d, 1H, J = 8.8 Hz), 5.31 (bs, 2H), 2.88 (bt, 2H, J = 7.4 Hz).

Step D: Preparation of 2-methylthio-3-propyl-4-benzyloxybenzaldehyde

A solution of 2-chloro-3-propyl-4-benzyloxybenzaldehyde (Step C; 0.683 grams) in dry DMF (7 mL) was treated with sodium methanethiolate (0.166 grams). The solution was stirred at 50°C for 3 hours. The reaction mixture was partitioned between isopropyl acetate and pH 7 buffer. The organic was washed 3 times with water, then dried over magnesium sulfate. Filtration and concentration afforded an oil which was chromatographed over silica gel to afford the title compound.

- 50 -

NMR (acetone) δ 10.61 (s, 1H), 7.79 (d, 1H, $J = 8.8$ Hz), 7.52-7.45 (m, 5H), 7.24 (d, 1H, $J = 8.8$ Hz), 5.29 (bs, 2H), 3.05 (bt, 2H, $J = 7.6$ Hz), 2.38 (s, 3H).

Step E: Preparation of 1-(2-methylthio-3-propyl-4-benzyloxy)-
phenyl-1-propanol

A solution of 2-methylthio-3-propyl-4-benzyloxy-benzaldehyde (Step D; 324 mg) in dry diethyl ether (3 mL) was added dropwise to a -78°C solution of 1M ethyl magnesium bromide in diethyl ether (2.5 mL). The reaction was stirred for 15 minutes, then allowed to warm to -10°C . The solution was treated with saturated aqueous ammonium chloride (2 mL), then allowed to warm to 25°C . The reaction was partitioned between isopropyl acetate and water. The organic was dried over magnesium sulfate, filtered and evaporated to an oil which was chromatographed over silica gel to afford the desired product.

NMR (acetone) δ 7.09 (d, 1H, $J = 8.9$ Hz), 5.31 (vbm, 1H), 5.13 (bs, 2H), 4.00 (vbs, 1H), 3.02 (bm, 2H), 2.24 (s, 3H).

Step F: Preparation of 2-methylthio-3-propyl-4-benzyloxypropio-
phenone

A -55°C solution of trifluoroacetic anhydride (0.291 mL) in dry methylene chloride (2 mL) was treated dropwise with a solution of dry DMSO (0.292 mL) in methylene chloride (1 mL). The reaction was stirred for 15 minutes, then treated with a solution of 1-(2-methylthio-3-propyl-4-benzyloxy)phenyl-1-propanol (Step E; 136 mg) in methylene chloride (2 mL). The solution was stirred for 30 minutes, then treated dropwise with dry triethylamine (1.15 mL). The mixture was stirred for 1 hour as it was allowed to warm to 25°C . The reaction was partitioned between isopropyl acetate and pH 7 buffer. The organic layer was dried over magnesium sulfate, filtered and concentrated to an

- 51 -

oil which was chromatographed over silica gel to afford the title compound.

NMR (acetone) δ 7.16 (d, 1H, $J = 8.8$ Hz), 7.11 (d, 1H, $J = 8.8$ Hz), 5.20 (bs, 2H), 3.00 (bt, 2H, $J = 7.4$ Hz), 2.88 (quart, 2H, $J = 7.2$ Hz), 2.27 (s, 3H).

Step G: Preparation of 2-methylthio-3-propyl-4-benzyloxypropio-
phenone oxime

Using the method of Example 1, Step C, substituting 2-methylthio-3-propyl-4-benzyloxypropio-phenone (Step F) as the starting material, the title compound was obtained.

NMR (major isomer, acetone) δ 9.91 (vbs, 1H), 7.07 (d, 1H, $J = 8.7$ Hz), 7.03 (d, 1H, $J = 8.7$ Hz), 5.16 (bs, 2H), 3.02 (bt, 2H, $J = 7.6$ Hz), 2.79 (quart, 2H, $J = 7.4$ Hz), 2.22 (s, 3H).

Step H: Preparation of 3-ethyl-6-benzyloxy-7-propylbenz-[4,5]-
isothiazole

A solution of 2-methylthio-3-propyl-4-benzyloxypropio-phenone oxime (Step G; 86 mg) in dry pyridine (2 mL) was treated with acetic anhydride (0.050 mL). The solution was refluxed for 4 hours. Three-quarters of the solvent was removed *in vacuo*. The remaining reaction mixture was partitioned between isopropyl acetate and 0.1N HCl. The organic was washed 3 times more with 0.1N HCl, then once with water. The organic was dried over magnesium sulfate, filtered and concentrated to an oil. Silica gel chromatography afforded the title compound.

NMR (acetone) δ 7.88 (bd, 1H, $J = 8.9$ Hz), 7.54-7.30 (m, 6H), 5.30 (bs, 2H), 3.04 (b quart, 2H, $J = 7.3$ Hz), 2.86 (bt, 2H, $J = 7.5$ Hz).

Step I: Preparation of 3-ethyl-6-hydroxy-7-propyl-benz-[4,5]-
isothiazole

- 52 -

Using the method of Example 3, Step E, substituting 3-ethyl-6-benzyloxy-7-propylbenz-[4,5]-isothiazole (Step H) as the starting material, the title compound was obtained.

NMR (acetone) δ 8.93 (vbs, 1H), 7.72 (d, 1H, $J = 8.8$ Hz), 7.08 (d, 1H, $J = 8.8$ Hz), 3.03 (quart, 2H, $J = 7.4$ Hz), 2.80 (bt, 2H, $J = 7.7$ Hz).

Step K: Preparation of 3-ethyl-6-(3-bromopropoxy)-7-propylbenz-[4,5]-isothiazole

Using the method of Example 1, Step A, substituting 3-ethyl-6-hydroxy-7-propylbenz-[4,5]-isothiazole (Step J) as the starting material, the title compound was obtained.

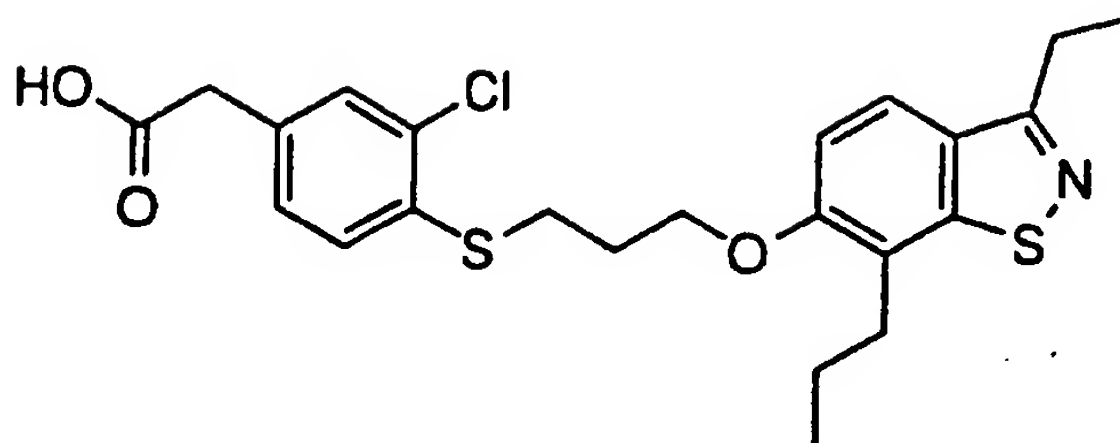
NMR (acetone) δ 7.90 (d, 1H, $J = 8.9$ Hz), 7.28 (d, 1H, $J = 8.9$ Hz), 4.31 (t, 2H, $J = 5.6$ Hz), 3.75 (t, 2H, $J = 6.5$ Hz), 3.04 (quart, 2H, $J = 7.3$ Hz), 2.82 (bt, 2H, $J = 7.5$ Hz).

Step L: Preparation of methyl 3-chloro-4-(3-(3-ethyl-7-propyl-6-benz-[4,5]-isothiazoloxo)propylthio)phenylacetate

Using the method of Example 1, Step B, substituting 3-ethyl-6-(3-bromopropoxy)-7-propylbenz-[4,5]-isothiazole (Step K) as the starting material, the title compound was obtained.

NMR (acetone) δ 7.90 (d, 1H, $J = 8.8$ Hz), 7.25 (overlapping d and dd, 2H, $J_d = 8.8$ Hz), 4.33 (t, 2H, $J = 5.7$ Hz), 3.63 (two overlapping s, 5H), 3.29 (t, 2H, $J = 7.4$ Hz), 3.04 (quart, 2H, $J = 7.6$ Hz), 2.83 (bt, 2H, $J = 7.5$ Hz).

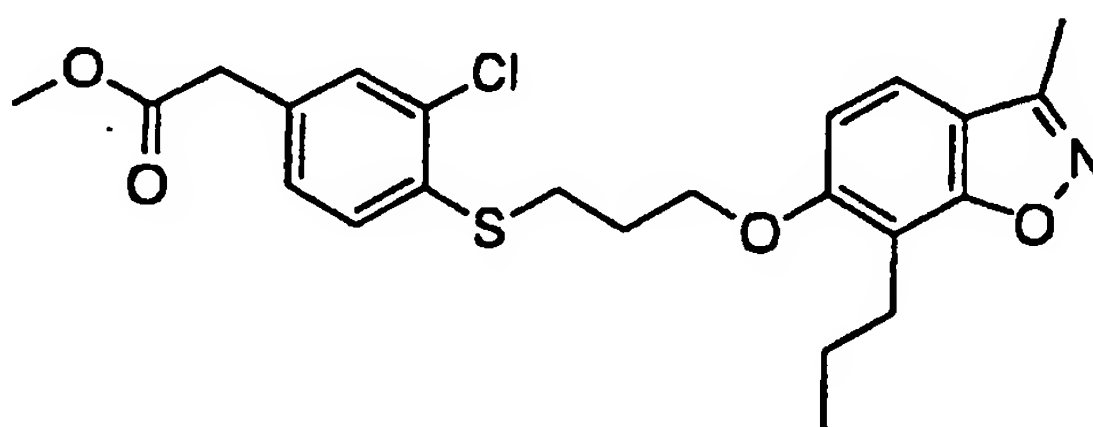
- 53 -

Example 6

3-chloro-4-(3-(3-ethyl-7-propyl-6-benz-[4,5]-isothiazole)oxy)propylthio phenylacetic acid

Using the method of Example 2, substituting methyl 3-chloro-4-(3-(3-ethyl-7-propyl-6-benz[4,5]isothiazoloxy)propylthio)phenylacetate (Example 5) as the starting material, the title compound was obtained.

NMR (acetone) δ 7.90 (d, 1H, $J = 8.8$ Hz), 7.26 (overlapping d and dd, 2H, $J_d = 8.8$ Hz), 4.33 (t, 2H, $J = 5.7$ Hz), 3.63 (s, 2H), 3.29 (t, 2H, $J = 7.4$ Hz), 3.05 (quart, 2H, $J = 7.6$ Hz), 2.83 (bt, 2H, $J = 7.5$ Hz).

Example 7

Methyl 3-chloro-4-(3-(3-methyl-7-propyl-6-benz-[4,5]-isoxazoloxy)propylthio)phenylacetate

Step A: Preparation of 3-methyl-6-hydroxy-7-propylbenz-[4,5]-isoxazole

- 54 -

A solution of 2,4-dihydroxy-3-propylacetophenone (1.008 grams) in dry methanol (10mL) was treated with hydroxylamine hydrochloride (1.803 grams) and anhydrous sodium acetate (2.127 grams). The mixture was refluxed 4 hours. HPLC analysis indicated the complete disappearance of starting material. The reaction was partitioned between isopropyl acetate and pH 7 buffer. The organic was dried over magnesium sulfate, filtered and evaporated to a solid. Acetic anhydride (11 mL) was added and the solution stirred at ambient temperature for 14 hours. The solvent was removed *in vacuo* and the residue partitioned between isopropyl acetate and pH 7 buffer. The organic was dried over magnesium sulfate, filtered and concentrated to a residue. Pyridine (12 mL) was added and the solution refluxed for 3 hours. The solvent was removed *in vacuo* and the residue partitioned between isopropyl acetate and 0.1 N HCl. The organic was washed with 0.1 N HCl and dried over magnesium sulfate. The organic was filtered and concentrated to a residue which was chromatographed over silica gel to afford the title compound.

NMR (CDCl₃) δ 7.28 (d, 1H, J = 8.8 Hz), 6.80 (d, 1H, J = 8.8 Hz), 5.33 (vbs, 1H), 2.83 (bt, 2H, J = 7.6 Hz), 2.50 (s, 3H).

Step B: Preparation of 3-methyl-6-(3-bromopropyl)oxy-7-propylbenz-[4,5]-isoxazole

Using the method of Example 1, step A, substituting 3-methyl-6-hydroxy-7-propylbenz-[4,5]-isoxazole (Step A) as the starting material, the title compound was obtained.

NMR (CDCl₃) δ 7.38 (d, 1H, J = 9.0 Hz), 6.92 (d, 1H, J = 9.0 Hz), 4.20 (t, 2H, J = 5.7 Hz), 3.64 (t, 2H, J = 6.4 Hz), 2.87 (bt, 2H, J = 7.6 Hz), 2.51 (s, 3H).

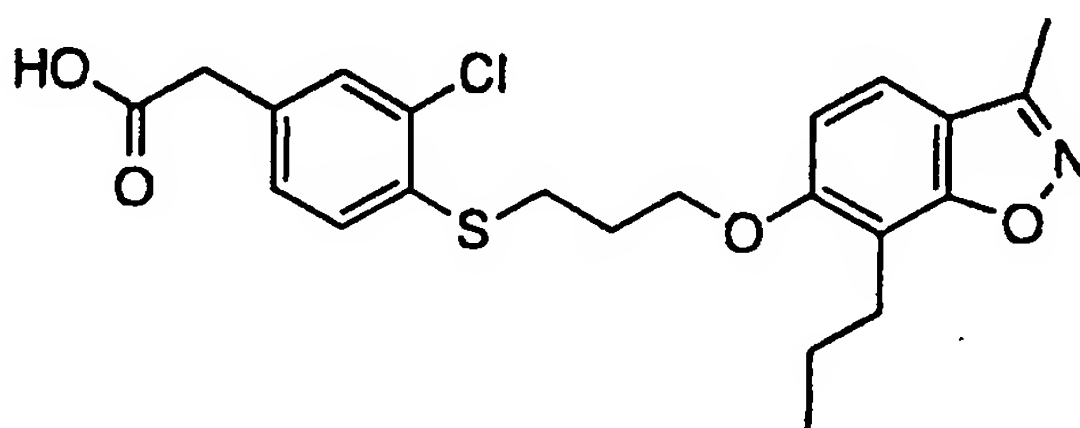
Step C: Preparation of methyl 3-chloro-4-(3-(3-methyl-7-propyl-6-benz-[4,5]-isoxazoloxy)propylthio)phenylacetate

- 55 -

Using the method of Example 1, step B, substituting 3-methyl-6-(3-bromopropyl)oxy-7-propyl-benz-[4,5]-isoxazole (Step C) as the starting material, the title compound was obtained.

NMR (CDCl₃) δ 7.35 (d, 1H, J = 8.6 Hz), 7.10 (dd, 1H, J = 8.1, 1.8 Hz), 6.89 (d, 1H, J = 8.6 Hz), 4.17 (t, 2H, J = 5.8 Hz), 3.68 (s, 3H), 3.16 (t, 2H, J = 7.1 Hz), 2.50 (s, 3H), 2.85 (bt, 2H, J = 7.5 Hz).

Example 8

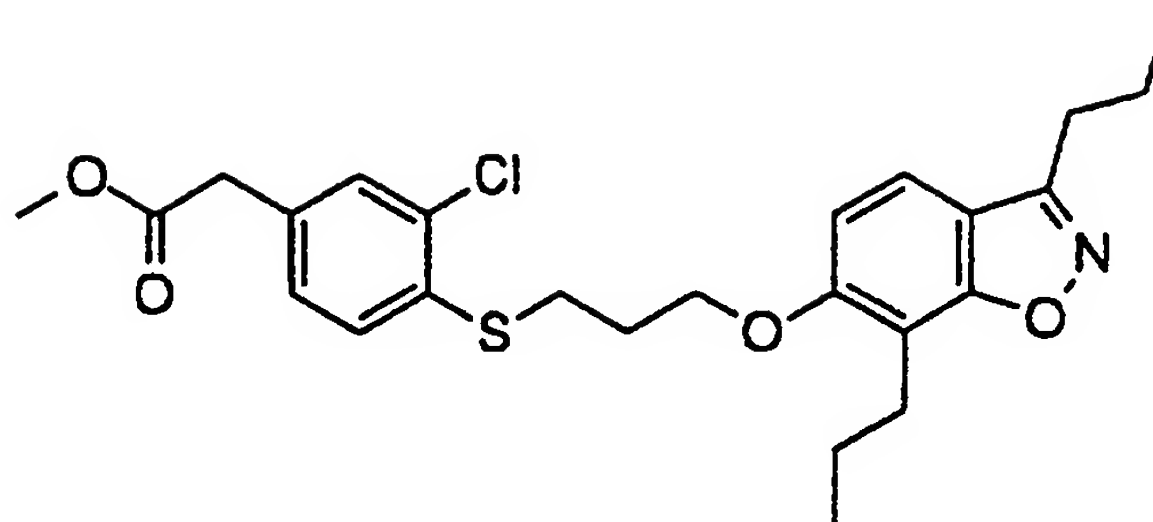


3-chloro-4-(3-(3-methyl-7-propyl-6-benz-[4,5]-isoxazoloxy)propylthio)-phenylacetic acid

Using the method of Example 2, substituting methyl 3-chloro-4-(3-(3-methyl-7-propyl-6-benz-[4,5]-isoxazoloxy)propylthio)phenylacetate (Example 7) as the starting material, the title compound was obtained.

NMR (CDCl₃) δ 7.34 (d, 1H, J = 8.7 Hz), 7.10 (dd, 1H, J = 8.1, 1.8 Hz), 6.89 (d, 1H, J = 8.7 Hz), 4.17 (t, 2H, J = 5.8 Hz), 3.58 (s, 2H), 3.17 (t, 2H, J = 7.2 Hz), 2.84 (bt, 2H, J = 7.5 Hz), 2.50 (s, 3H).

- 56 -

Example 9

Methyl 3-chloro-4-(3-(3,7-dipropyl-6-benz-[4,5]-isoxazole)oxy)-propylthio phenyl acetate

Step A: Preparation of 2-hydroxy-3-propyl-4-(3-bromopropoxy)-phenyl propyl ketone

Using the method of Example 1, step A, substituting 2,4-dihydroxy-3-propylphenyl propyl ketone as the starting material, the title compound was obtained.

NMR (CDCl₃) δ 7.61 (d, 1H, J = 8.8 Hz), 6.43 (d, 1H, J = 8.8 Hz), 4.16 (t, 2H, J = 5.7 Hz), 3.60 (t, 2H, J = 6.4 Hz), 2.87 (t, 2H, J = 7.4 Hz), 2.61 (bt, 2H, J = 7.5 Hz).

Step B: Preparation of methyl 3-chloro-4-(3-(2-propyl-3-hydroxy-4-butyrophenoxy)propylthio)phenylacetate

Using the method of Example 1, step B, substituting 2-hydroxy-3-propyl-4-(3-bromopropoxy)phenyl propyl ketone as the starting material, the title compound was obtained.

NMR (CDCl₃) δ 7.61 (d, 1H, J = 9.0 Hz), 7.11 (dd, 1H, J = 8.1, 1.8 Hz), 6.41 (d, 1H, J = 8.9 Hz), 4.14 (t, 2H, J = 5.8 Hz), 3.68 (s, 3H), 3.13 (t, 2H, J = 7.6 Hz), 2.87 (t, 2H, J = 7.1 Hz), 2.60 (bt, 2H, J = 7.4 Hz).

Step C: Preparation of methyl 3-chloro-4-(3-(2-propyl-3-hydroxy-4-(1-hydroxyliminobutyl)phenoxy)propylthio)phenylacetate

- 57 -

Using the method of Example 1, step C, substituting methyl 3-chloro-4-(3-(2-propyl-3-hydroxy-4-butyrophenoxy)propylthio)phenyl-acetate as the starting material, the title compound was obtained.

NMR (CDCl₃) δ 7.12 (dd, 1H, J = 8.0, 1.8 Hz), 6.43 (d, 1H, J = 8.9 Hz), 4.09 (t, 2H, J = 5.7 Hz), 3.69 (s, 3H), 3.13 (t, 2H, J = 7.3 Hz), 2.79 (bt, 2H, J = 7.9 Hz), 2.65 (bt, 2H, J = 7.6 Hz).

Step D: Preparation of methyl 3-chloro-4-(3-(2-propyl-3-hydroxy-4-(1-acetoxyiminobutyl))phenoxy)propylthio phenyl acetate

Using the method of Example 1, step D, substituting methyl 3-chloro-4-(3-(2-propyl-3-hydroxy-4-(1-hydroxyliminobutyl)phenoxy)-propylthio)phenylacetate as the starting material, the title compound was obtained.

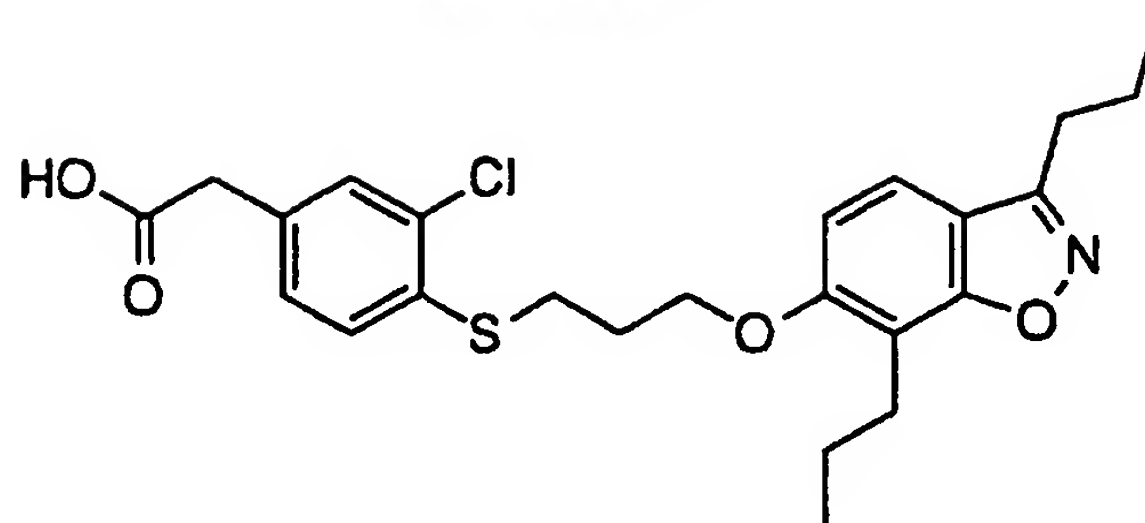
NMR (CDCl₃) δ 7.11 (dd, 1H, J = 7.9, 1.8 Hz), 6.43 (d, 1H, J = 8.8 Hz), 4.09 (t, 2H, J = 5.8 Hz), 3.69 (s, 3H), 3.13 (t, 2H, J = 7.2 Hz), 2.82 (bt, 2H, J = 7.8 Hz), 2.68 (bt, 2H, J = 7.7 Hz).

Step E: Preparation of methyl 3-chloro-4-(3-(3,7-dipropyl-6-benz-[4,5]-isoxazoloxy)propylthio)phenyl acetate

Using the method of Example 1, step E, substituting methyl 3-chloro-4-(3-(2-propyl-3-hydroxy-4-(1-acetoxyiminobutyl) phenoxy) propylthio)phenylacetate as the starting material, the title compound was obtained.

NMR (CDCl₃) δ 7.37 (d, 1H, J = 8.7 Hz), 7.10 (dd, 1H, J = 8.1, 1.8 Hz), 6.88 (d, 1H, J = 8.7 Hz), 4.17 (t, 2H, J = 5.9 Hz), 3.68 (s, 3H), 3.15 (t, 2H, J = 7.2 Hz), 2.90-2.81 (2 overlapping t, 4H).

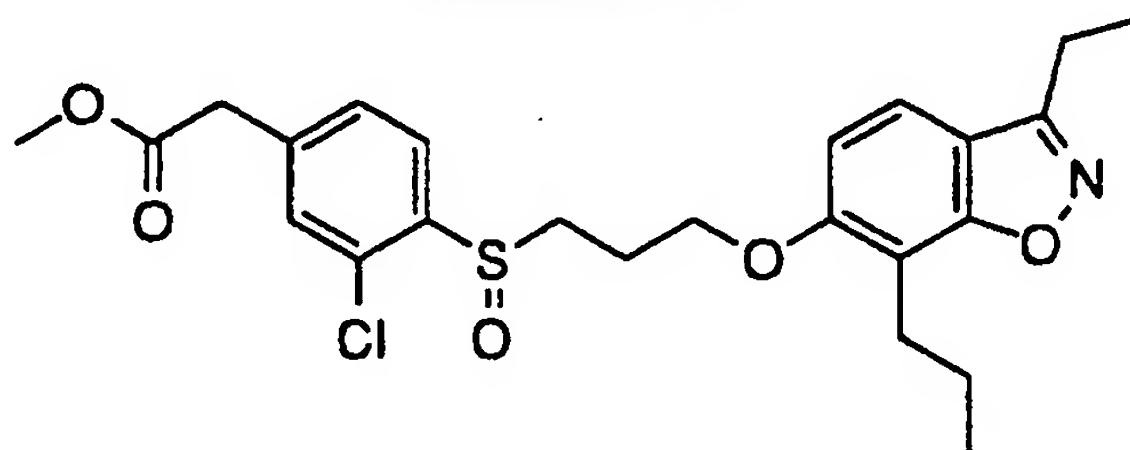
- 58 -

Example 10

3-chloro-4-(3-(3,7-dipropyl-6-benz-[4,5]-isoxazoloxy)propylthio)phenyl-acetic acid

Using the method of Example 2, substituting methyl 3-chloro-4-(3-(3,7-dipropyl-6-benz-[4,5]-isoxazoloxy)propylthiophenylacetate as the starting material, the title compound was obtained.

NMR (CDCl₃) δ 7.38 (d, 1H, J = 8.8 Hz), 7.10 (dd, 1H, J = 8.1, 1.8 Hz), 6.87 (d, 1H, J = 8.8 Hz), 4.17 (t, 2H, J = 5.8 Hz), 3.57 (s, 2H), 3.16 (t, 2H, J = 7.1 Hz) 2.91-2.81 (2 overlapping t, 4H).

Example 11

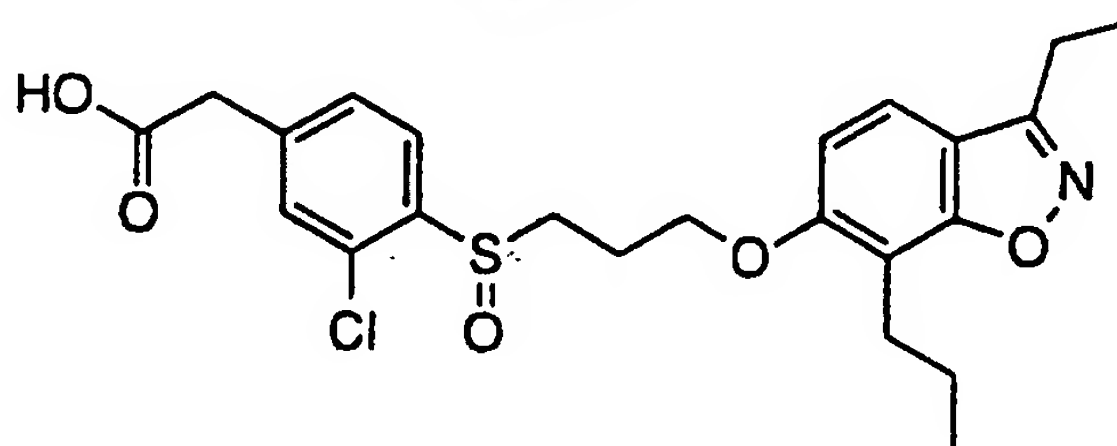
Methyl 3-chloro-4-(3-(3-ethyl-7-propyl-6-benz-[4,5]-isoxazoloxy)propylthio)phenylacetate S-oxide

A 25°C solution of methyl 3-chloro-4-(3-(3-ethyl-7-propyl-6-benz-[4,5]-isoxazoloxy)propylthio)phenylacetate (Example 1; 57 mg) in methanol (2 mL) was treated with 80% magnesium monoperoxyphthalate hexahydrate (49 mg). The mixture was stirred for 1 hour. The reaction was partitioned between isopropyl acetate and pH

7 buffer. The organic was washed once with water and dried over magnesium sulfate. Filtration and concentration afforded a solid which was purified by chromatography over silica gel to afford the title compound.

NMR (CDCl₃) δ 7.83 (d, 1H, J = 8.8 Hz), 7.41 (dd, 1H, J = 8.1, 1.8 Hz), 6.82 (d, 1H, J = 8.8 Hz), 4.16 (dtt, 2H), 3.70 (s, 3H), 3.35 (ddd, 1H), 2.98 (ddd, 1H), 2.92 (quart, 2H, J = 7.5 Hz), 2.79 (bt, 2H, J = 7.6 Hz).

Example 12

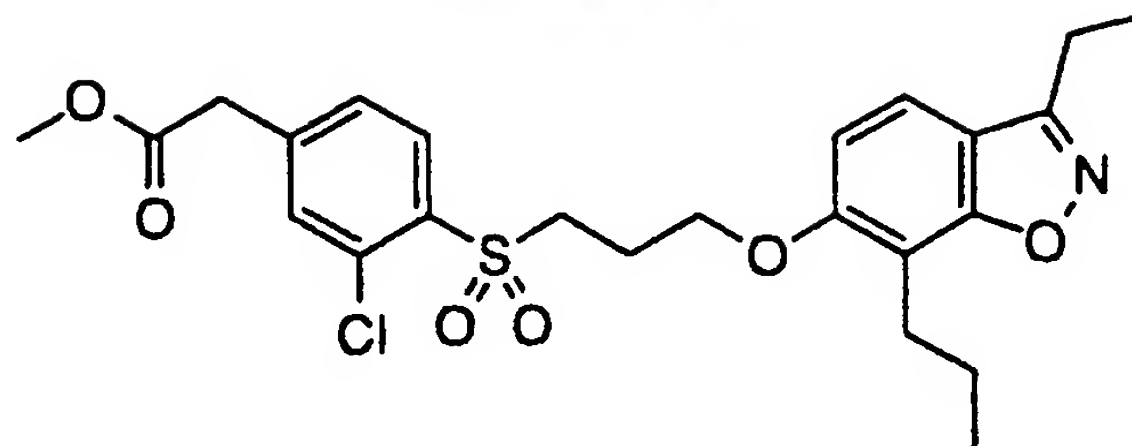


3-chloro-4-(3-(3-ethyl-7-propyl-6-benz-[4,5]-isoxazoloxy)propylthio)-phenylacetic acid S-oxide

Using the method of Example 2, substituting methyl 3-chloro-4-(3-(3-ethyl-7-propyl-6-benz-[4,5]-isoxazoloxy)propylthio)phenylacetate S-oxide (Example 11) as the starting material, the title compound was obtained.

NMR (acetone) δ 7.81 (d, 1H, $J = 8.9$ Hz), 7.59 (dd, 1H, $J = 8.1, 1.8$ Hz), 7.04 (d, 1H, $J = 9.0$ Hz), 4.27 (tt, $J = 5.7, 1.1, 1.1$ Hz), 3.78 (s, 2H), 3.39 (ddd, 1H), 3.03 (ddd, 1H), 2.94 (quart, 2H, $J = 7.8$ Hz), 2.82 (bt, 2H, $J = 7.9$ Hz).

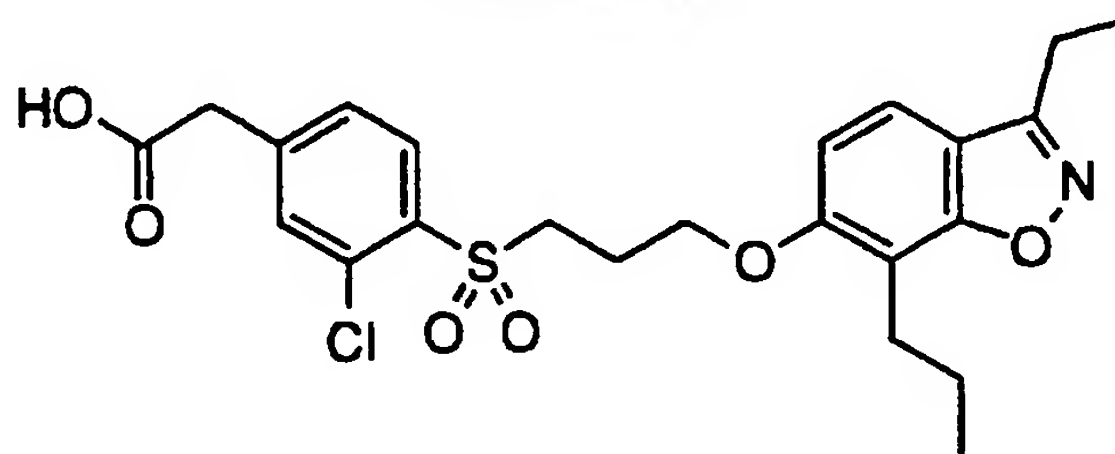
- 60 -

Example 13

Methyl 3-chloro-4-(3-(3-ethyl-7-propyl-6-benz-[4,5]-isoxazoloxy)propylthio)phenylacetate S,S-dioxide

A solution of methyl 3-chloro-4-(3-(3-ethyl-7-propyl-6-benz-[4,5]-isoxazoloxy)propylthio)phenylacetate S-oxide (Example 11; 34 mg) in methanol (1 mL) was treated with 80% magnesium monoperoxyphthalate hexahydrate (33 mg). The solution was stirred at 25°C for 16 hours. The reaction was partitioned between isopropyl acetate and pH 7 buffer. The organic was washed once with water, then dried over magnesium sulfate. Filtration and evaporation afforded a solid which was chromatographed over silica gel to give the title compound.

NMR (CDCl₃) δ 8.05 (d, 1H, J = 8.9 Hz), 7.36 (dd, 1H, J = 8.1, 1.9 Hz), 6.77 (d, 1H, J = 8.9 Hz), 4.12 (t, 2H, J = 5.7 Hz), 3.71 (s, 3H), 3.67 (bt, 2H, J = 7.3 Hz), 2.92 (quart, 2H, J = 7.4 Hz), 2.80 (bt, J = 7.6 Hz).

Example 14

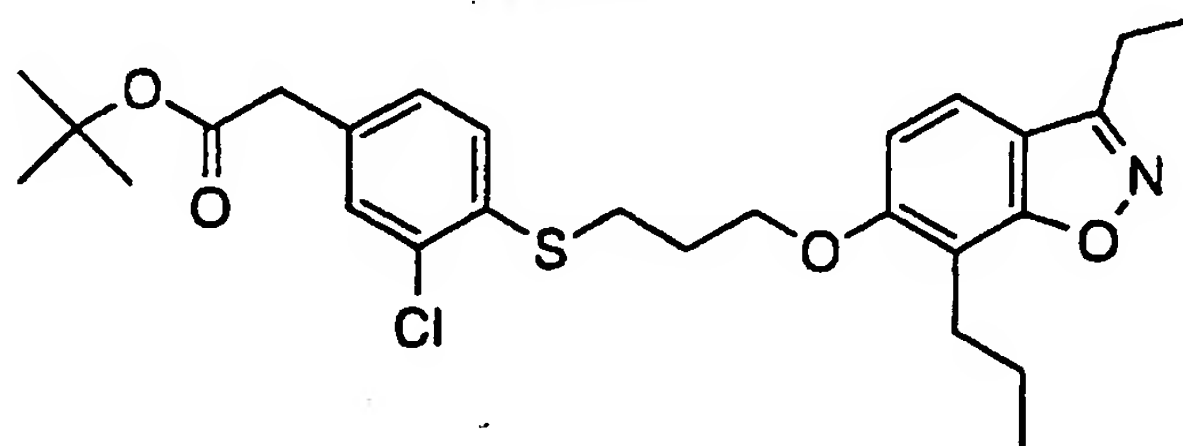
3-Chloro-4-(3-(3-ethyl-7-propyl-6-benz-[4,5]-isoxazole)oxy)-propylthio phenylacetic acid S,S-dioxide

- 61 -

Using the method of Example 2, substituting methyl 3-chloro-4-(3-(3-ethyl-7-propyl-6-benz-[4,5]-isoxazoloxy)propylthio)phenylacetate S,S-dioxide (Example 13) as the starting material, the title compound was obtained.

NMR (CDCl₃) δ 8.09 (d, 1H, J = 8.8 Hz), 7.38 (dd, 1H, J = 8.1, 1.9 Hz), 6.80 (d, 1H, J = 8.8 Hz), 4.13 (t, 2H J = 5.6 Hz), 3.69 (s, 2H), 3.65 (bt, 2H, J = 7.2 Hz), 2.93 (quart, 2H, J = 7.5 Hz), 2.80 (bt, J = 7.6 Hz).

Example 15

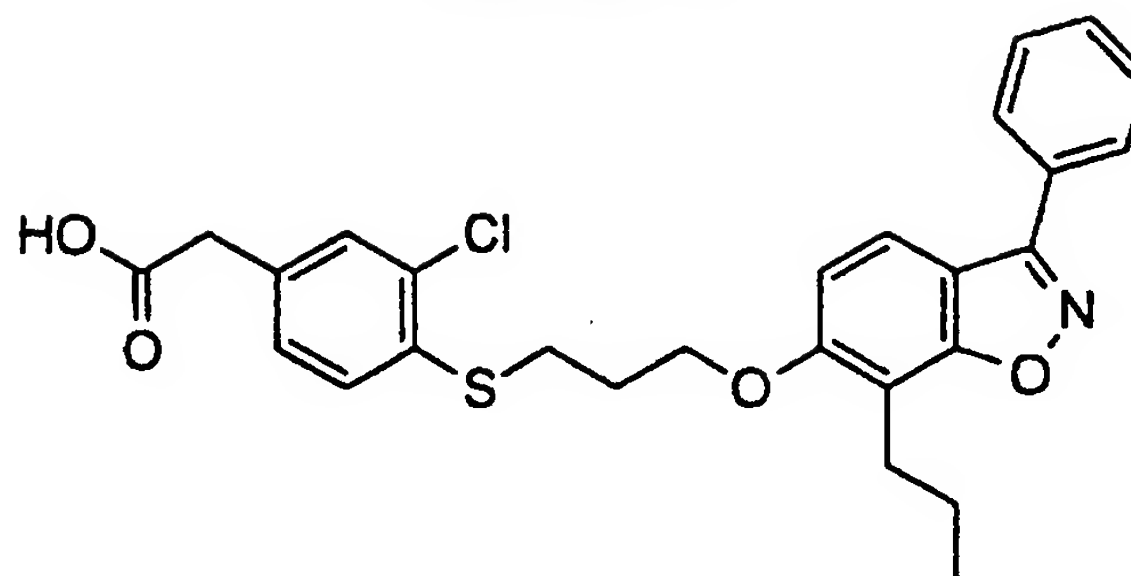


tert-Butyl 3-chloro-4-(3-(3-ethyl-7-propyl-6-benz-[4,5]-isoxazoloxy)-propylthio)phenyl acetate

A solution of 3-chloro-4-(3-(3-ethyl-7-propyl-6-benz-[4,5]-isoxazoloxy)propylthio)phenylacetic acid (Example 2; 0.073 grams) in dry toluene (1.0 mL) was treated with dimethylformamide bis-*tert*-butyl acetal (0.780 mL). The solution was heated at 70°C for 24 hours. The reaction was partitioned between isopropyl acetate and pH 4 buffer. The organic layer was dried over magnesium sulfate and filtered. Concentration afforded a solid which was chromatographed over silica gel to afford the title compound.

NMR (CDCl₃) δ 7.38 (d, 1H, J = 8.8 Hz), 7.10 (dd, 1H, J = 8.1, 1.8 Hz), 6.87 (d, 1H, J = 8.8 Hz), 4.17 (t, 2H, J = 5.8 Hz), 3.43 (s, 2H), 3.16 (t, 2H, J = 7.1 Hz), 2.94 (quart, 2H, J = 7.6 Hz), 2.85 (bt, 2H, J = 7.5 Hz), 1.40 (s overlapping with downfield peak of t, 12H total).

- 62 -

Example 16

3-Chloro-4-(3-(3-phenyl-7-propyl-6-benz-[4,5]-isoxazoloxy)-propylthio)phenylacetic acid

Step 1A

A solution of 3-chloro-4-dimethylcarbamoylthiophenyl acetic acid methyl ester (10.028 grams; 34.848 mmol) in dry MeOH (90 mL) was treated with a solution of sodium methoxide (4.37 M; 11.16 mL; 48.788 mmol). The reaction was refluxed for 2 hours. The reaction mixture was cooled to 20° C and transferred to a dropping funnel. The dropping funnel was placed atop a flask containing a solution of dibromopropane (14.15 mL; 139.392 mmol) in dry MeOH (50 mL). The contents of the dropping funnel were added to the flask dropwise, and the solution stirred for 2 hours. The reaction mixture was partitioned between isopropyl acetate and pH 4 buffer. The layers were separated and the organic washed once with water. The organic was dried over magnesium sulfate, filtered and concentrated. Silica gel chromatography afforded 3-chloro-4-(3-bromopropyl)thiophenyl acetic acid methyl ester.

Step 1

Commercially available 4-allyloxy-2-hydroxybenzophenone (15 g) was rearranged by heating under reflux in ortho-dichlorobenzene (60 mL) for 26 hours. The product was isolated by dilution of the reaction mixture with 5 volumes hexanes to give a crystalline product as fine needles.

- 63 -

Characteristic NMR Resonances; ^1H NMR 400MHz (CDCl_3); 7.62-7.59 (m, 2H), 7.56-7.52 (m, 2H), 7.49-7.44 (m, 2H), 7.40 (d, 1H, $J=8.9$ Hz), 6.34 (d, 1H, $J=8.8$ Hz), 6.02 (ddt, 1H, $J=17.21, 10.1, 6.2$ Hz), 5.72 (s, 1H, phenol OH), 5.14-5.24 (m, 2H), 3.53 (d with fine splitting, 2H, $J=6.2$ Hz).

Step 2

A solution of 2,4-dihydroxy-3-(2-propenyl)benzophenone (3 g) was reduced under ~ 1 atm H_2 in ethyl acetate (100 mL) over 10% Pd/C catalyst (0.3 grams) for 3 hours. The product was purified by crystallization from methanol/water. The product is obtained as small yellow plates.

Characteristic NMR Resonances; ^1H NMR 400MHz (CDCl_3); 7.61-7.59 (m, 2H), 7.55-7.51 (m, 1H), 7.48-7.44 (m, 2H), 7.33 (d, 1H, $J=8.8$ Hz), 6.29 (d, 1H, $J=8.8$ Hz), 5.51 (s, 1H, phenol OH), 2.66 (dd, 2H, $J=7.6, 9.3$ Hz), 1.61 (sext, 2H, $J=7.7$ Hz), 0.99 (t, 3H, $J=7.3$ Hz).

Step 3

The 2,4-dihydroxy-3-propylbenzophenone (2.5 g, 1.0 Eq, 9.8 mmol) was converted to the oxime with $\text{NH}_2\text{OH}\cdot\text{HCl}$ (2.7 g, 4.0 Eq, 39 mmol) and NaOAc (3.21 g, 4.0 Eq, 39 mmol) as in Example 7 Step A. The oxime was purified by elution from a silica gel column (180 g E. Merck 40-63 μ) with 97 : 3 Toluene : EtOAc. The product oxime (1.82 g) was further treated as in Example 7 Step A with acetic anhydride (15 ml) and subsequent reflux in pyridine (15 ml). The cooled reaction mixture was poured into 2 N HCl and EtOAc. The aqueous phase was extracted with EtOAc and washed with sat'd aq NaHCO_3 , followed by sat'd aq NaCl. The EtOAc extracts were dried over Na_2SO_4 and reduced *i. vac.* The residue was taken up in refluxing toluene (50 ml). The product benzisoxazole is obtained as colorless crystals upon cooling to RT.

Characteristic NMR Resonances; ^1H NMR 400MHz (CDCl_3); 7.92-7.89 (m, 2H), 7.57 (d, 1H, $J=8.5$ Hz), 7.55-7.49 (m, 3H), 6.86 (d, 1H, $J=8.6$ Hz), 5.14 (s, 1H, phenol OH), 2.90 (dd, 2H, $J=8.9, 7.6$ Hz), 1.76 (sext, 2H, $J=7.5$ Hz), 1.01 (t, 3H, $J=7.3$ Hz).

- 64 -

MS CI NH₃ M+1 254.1

Step 4

The hydroxy-3-phenylbenzisoxazole (50 mg, 1.0 Eq, 0.195 mmol) was dissolved in DMF (0.4 ml) with the bromide (73 mg, 1.1 Eq, 0.22 mmol) and CsCO₃ (62 mg, 1.0 Eq, 0.195 mmol). The suspension was stirred 3 Hrs at RT. The mixture was poured into 0.2 N HCl and EtOAc. The aqueous phase was extracted with EtOAc and the EtOAc extracts washed with sat'd aq NaCl. The extracts were dried over MgSO₄ and reduced *i. vac.* The product was purified by elution from a silica gel column (4 g E. Merck 40-63 μ) with toluene : hexanes : EtOAc 60 : 37 : 3.

Characteristic NMR Resonances; ¹H NMR 400MHz (CDCl₃); 7.91-7.93 (m, 2H), 7.64 (d, 2H, J=8.7 Hz), 7.51-7.53 (m, 3H), 7.30 (d, 1H, 1.8 Hz), 7.28 (d, 1H, J=8.1 Hz), 7.12 (dd, 1H), 6.96 (d, 1H, J=8.8), 4.21 (t, 2H, J=5.9 Hz), 3.68 (s, 3H), 3.54 (s, 2H), 3.17 (t, 2H, J=7.1 Hz), 2.92 (dd, 2H), 2.20 (pent, 2H), 1.72 (sext, 2H, J=7.5 Hz), 0.97 (t, 3H, J= 7.3 Hz).

MS ESI M+1 510.1.

Step 5

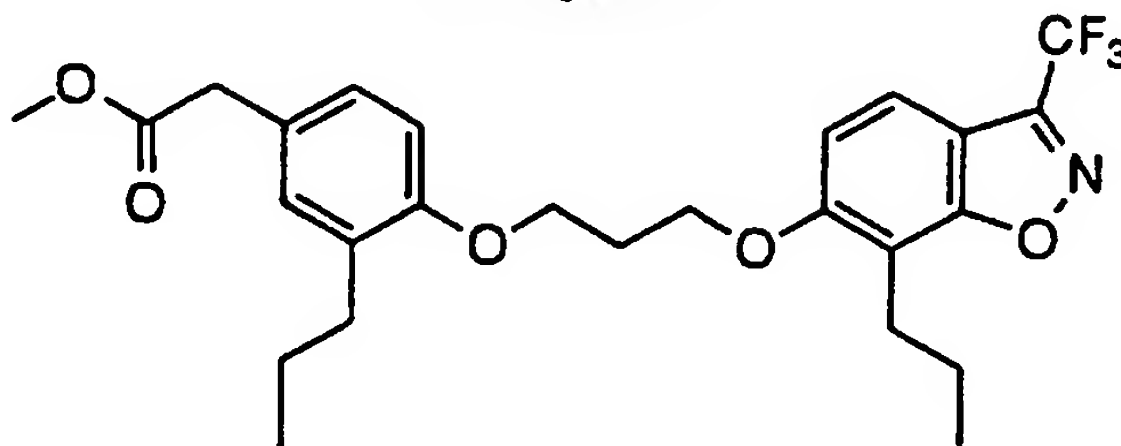
The ester (43.8 mg, 1 Eq, 0.086 mmol) was dissolved in approximately 1 ml 2 : 1 dioxane : H₂O. 1.5 M Aqueous LiOH (120 μl, 2.0 Eq, 0.180 mmol) was added dropwise at RT and the mixture stirred 3/4 Hr. The reaction mixture was diluted into 0.2 N HCl and EtOAc. The aqueous phase was extracted with EtOAc and the EtOAc extracts washed with sat'd aq NaCl. The extracts were dried over MgSO₄ and reduced *i. vac.*

The crude acid can be purified by crystallization from methanol.

Characteristic NMR Resonances; ¹H NMR 400MHz (CDCl₃);); 7.92 (m, 2H), 7.64 (d, 1H, J=8.8 Hz), 7.52 (m, 3H), 7.3 (m, 2H), 7.13 (dd, 1H, J=1.9, 8.1 Hz), 6.96 (d, 1H, J=8.8 Hz), 4.21 (t, 2H, J=5.8 Hz), 3.58

- 65 -

(s, 2H), 3.18 (t, 2H, J=7.2 Hz), 2.91 (dd, 2H, J=6.5, 7.7 Hz), 2.2 (pent, 2H, J=5.8 Hz), 1.71 (sext, 2H, J=7.5 Hz), 0.97 (t, 3H, J=7.4Hz).
MS ESI M+1 496.1.

Example 17

Methyl 3-propyl-4-(3-(3-trifluoromethyl-7-propyl-6-benz-[4,5]-isoxazoloxy)-propylthio)phenylacetate

Step A: Preparation of methyl 4-alloxyphenylacetate

A solution of methyl 4-hydroxyphenylacetate (3.2 grams) in 2-butanone (70 mL) was treated with allyl bromide (2.0 mL) and potassium carbonate (3.5 grams). The mixture was refluxed overnight. The reaction mixture was cooled to room temperature and partitioned between isopropyl acetate and pH 4 buffer. The organic layer was separated, washed with water, dried over MgSO₄, and concentrated. Column Chromatography (silica gel 60, 50% methylene chloride in hexane) gave the title compound.

¹H NMR(400MHz, CDCl₃): δ 7.16 (d, 2H, J = 8.7 Hz), 6.85 (d, 2H, J = 8.7 Hz), 6.04 (m, 1H), 5.4-5.2 (m, 2H), 4.5 (m, 2H), 3.66 (s, 3H), 3.54 (s, 2H).

Step B: Preparation of methyl 3-allyl-4-hydroxyphenylacetate

A solution of methyl 4-alloxyphenylacetate (3.1 grams) in dry ortho-dichlorobenzene (50 mL) was refluxed for 25 hours. The solvent was removed under reduced pressure, and the residue was purified by chromatography (silica gel, 50% methylene chloride in hexane) to afford the title compound.

- 66 -

¹H NMR(400MHz, CDCl₃): δ 7.01 (m, 2H), 6.71 (d, 1H, J = 7.4 Hz), 5.27 (s, 1H), 5.12 (m, 2H), 3.67 (s, 3H), 3.52 (s, 2H), 3.35 (m, 2H).

Step C: Preparation of methyl 3-propyl-4-hydroxyphenylacetate

A solution of methyl 3-propyl-4-hydroxyphenylacetate (1.71 grams) and palladium (10 wt.% on activated carbon) (0.27 grams) in ethyl acetate (30 mL) was hydrogenated at 50 PSI for 2 hours. The reaction mixture was filtered and concentrated to afford the tittle compound.

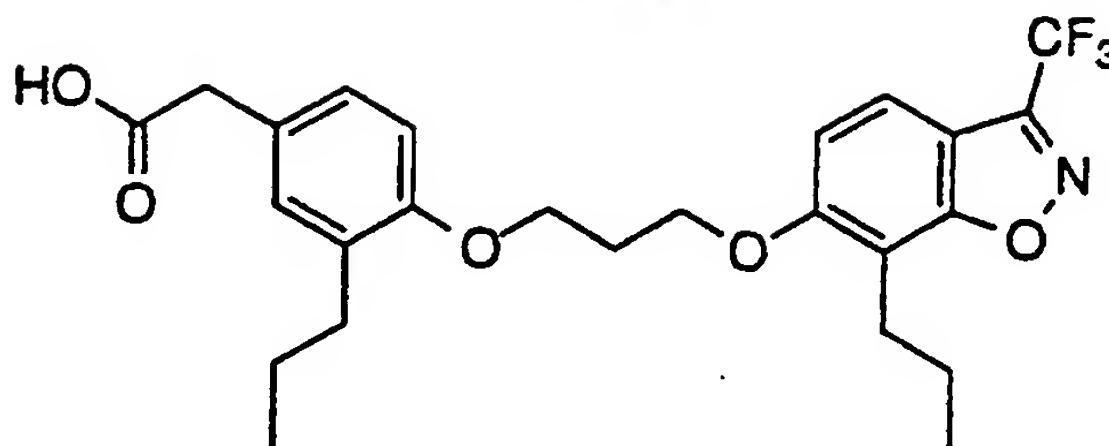
¹H NMR(400MHz, CDCl₃): δ 6.99 (d, 1H, J = 2.2 Hz), 6.95 (dd, 1H, J = 8.1, 2.2 Hz), 6.67 (d, 1H, J = 8.1 Hz), 4.83 (s, 1H), 3.66 (s, 3H), 3.51 (s, 2H), 2.53 (t, 2H, J = 7.6 Hz), 1.61 (hex, 2H, J = 7.5 Hz), 0.95 (t, 3H, J = 7.3 Hz).

Step D: Preparation of methyl 3-propyl-4-(3-(3-trifluoromethyl-7-propyl-6-benz-[4,5]-isoxazoloxy)-propylthio)phenylacetate

A solution of methyl 3-propyl-4-hydroxyphenylacetate (0.10 grams), 1-bromo-3-(3-trifluoromethyl-7-propyl-6-benz-[4,5]-isoxazoloxy)phenoxypropane (0.21 grams) and potassium carbonate (0.07 grams) in 2-butanone (4 mL). The mixture was refluxed overnight. The reaction mixture was cooled to room temperature and partitioned between isopropyl acetate and pH 4 buffer. The organic layer was separated, washed with water, dried over MgSO₄, and concentrated. Column Chromatography (silica gel 60, 50% methylene chloride in hexane) gave the tittle compound.

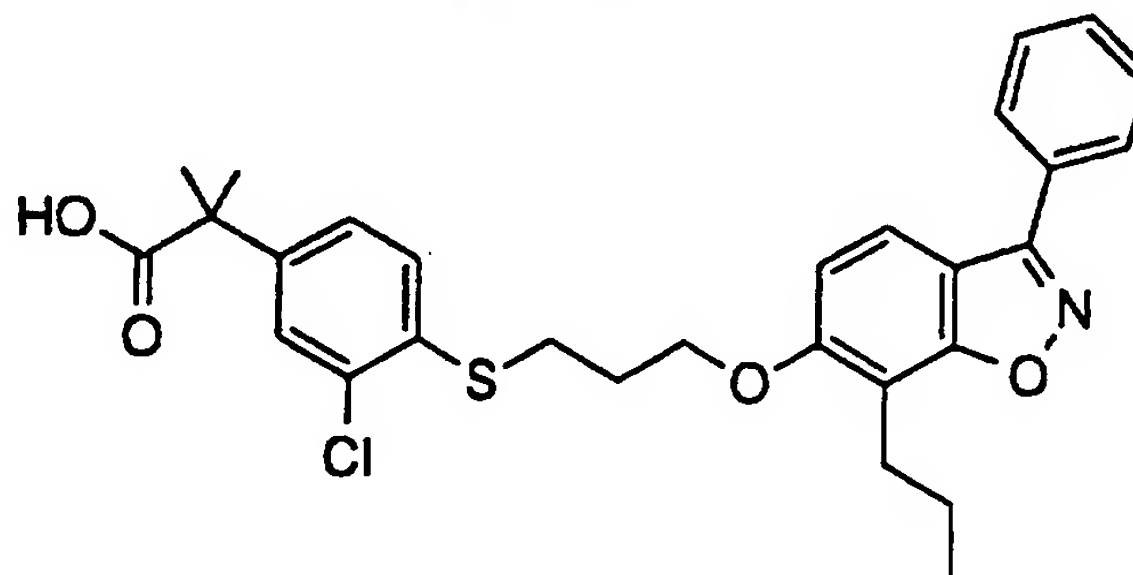
¹H NMR(400MHz, CDCl₃): δ 7.53 (d, 1H, J = 8.8 Hz), 7.03 (d, 1H, J = 8.9 Hz), 7.01 (m, 2H), 6.78 (d, 1H, J = 8.3 Hz), 4.30 (t, 2H, J = 6.1 Hz), 4.16 (t, 2H, J = 6.0 Hz), 3.65 (s, 3H), 3.52 (s, 2H), 2.87 (t, 2H, J = 7.5 Hz), 2.53 (t, 2H, J = 7.6 Hz), 2.32 (quint, 2H, J = 6.1 Hz), 1.66 (hex, 2H, J = 7.6 Hz), 1.55 (hex, 2H, J = 7.5 Hz), 0.91 (t, 3H, J = 7.3 Hz), 0.87 (t, 3H, J = 7.3 Hz).

- 67 -

Example 183-propyl-4-(3-(3-trifluoromethyl-7-propyl-6-benz-[4,5]-isoxazoloxo)-propylthio)phenylacetic acid

A solution of methyl 3-propyl-4-(3-(3-trifluoromethyl-7-propyl-6-benz-[4,5]-isoxazoloxo)-propylthio)phenylacetate (0.08 grams) in methanol (3 mL) was treated with a solution of LiOH in water (1.0 M, 0.32 mL). The solution was refluxed for 1 hour. The solution was partitioned between isopropyl acetate and 0.2 N HCl. The organic layer was separated, washed with water, dried over MgSO₄, and concentrated to afford the title compound.

¹H NMR (400MHz, CDCl₃): δ 7.53 (d, 1H, J = 8.8 Hz), 7.05 (d, 1H, J = 8.8 Hz), 7.02 (m, 2H), 6.79 (d, 1H, J = 8.3 Hz), 4.29 (t, 2H, J = 6.1 Hz), 4.16 (t, 2H, J = 6.0 Hz), 3.54 (s, 2H), 2.88 (t, 2H, J = 7.5 Hz), 2.52 (t, 2H, J = 7.6 Hz), 2.33 (quint, 2H, J = 6.1 Hz), 1.67 (hex, 2H, J = 7.6 Hz), 1.54 (hex, 2H, J = 7.5 Hz), 0.90 (t, 3H, J = 7.3 Hz), 0.86 (t, 3H, J = 7.3 Hz).

Example 192-methyl-2-(3-chloro-4-(3-(3-phenyl-7-propylbenz[4,5]isoxazol-6-oxo)propylthio)phenyl)propionic acid

- 68 -

1. 2-methyl-2-(3-chloro-4-dimethyl carbamoylthio)phenyl propionic acid methyl ester

A -78° C solution 2-(3-chloro-4-dimethylcarbamoylthio)-phenyl propionic acid methyl ester (0.378 grams; 1.25 mmol) in dry THF (2 mL) was treated with a solution of lithium bis(trimethylsilyl)amide (1.0M; 1.50 mL; 1.50 mmol). The reaction was stirred for 1 hour at -78° C, then allowed to warm to -10° C and stirred for 30 minutes. The solution was re-cooled to -78° C and treated dropwise with a solution of methyl iodide (0.094 mL; 1.50 mmol) in dry THF (0.5 mL). The reaction was stirred at -78° C for 30 minutes, then warmed to -10° C and stirred for an additional 30 minutes. The reaction mixture was partitioned between isopropyl acetate and pH 4 buffer. The layers were separated and the organic washed once with water. The organic was dried over magnesium sulfate, filtered and concentrated to an oil. Silica gel chromatography afforded 2-methyl-2-(3-chloro-4-dimethyl carbamoylthio)phenyl propionic acid methyl ester. NMR (CDCl₃): 7.54 (d, 1H, J = 8.2 Hz); 7.48 (d, 1H, J = 2.1 Hz); 7.24 (dd, 1H, J = 8.1, 2.0 Hz); 3.65 (s, 3H); 3.12 (vbs, 3H); 3.04 (vbs, 3H); 1.56 (s, 6H).

2. 2-methyl-2-(3-chloro-4-(3-bromopropyl)thio)phenyl propionic acid methyl ester

A solution of 2-methyl-2-(3-chloro-4-dimethylcarbamoylthio)-phenyl propionic acid methyl ester (0.403 grams; 1.27 mmol) in dry MeOH (4 mL) was treated with a solution of sodium methoxide (4.37 M; 0.407 mL; 1.78 mmol). The reaction was refluxed for 2 hours. The reaction mixture was cooled to 20° C and transferred to a dropping funnel. The dropping funnel was placed atop a flask containing a solution of dibromopropane (0.516 mL; 5.08 mmol) in dry MeOH (2 mL). The contents of the dropping funnel were added to the flask dropwise, and the solution stirred for 2 hours. The reaction mixture was partitioned between isopropyl acetate and pH 4 buffer. The layers were separated and the organic washed once with

- 69 -

water. The organic was dried over magnesium sulfate, filtered and concentrated. Silica gel chromatography afforded 2-methyl-2-(3-chloro-4-(3-bromopropyl)thio)phenyl propionic acid methyl ester. NMR (CDCl₃): 7.36 (d, 1H, J = 2.1 Hz); 7.26 (d, 1H, J = 8.3 Hz); 7.19 (dd, 1H, J = 8.2, 2.0 Hz); 3.66 (s, 3H); 3.55 (t, 2H, J = 6.3 Hz); 3.09 (t, 2H, J = 7.0 Hz); 2.18 (pent, 2H, J = 6.6 Hz).

3. 2-methyl-2-(3-chloro-4-(3-(3-phenyl-7-propyl-6-benz[4,5]isoxazole)oxypropyl)thio)phenyl propionic acid methyl ester

A solution of 2-methyl-2-(3-chloro-4-(3-bromopropyl)thio)phenyl propionic acid methyl ester (0.053 grams; 0.145 mmol) in dry DMF (1 mL) was treated with 3-phenyl-6-hydroxy-7-propylbenz[4,5]isoxazole (0.044 grams; 0.174 mmol). Cesium carbonate (0.057 grams; 0.174 mmol) was added and the reaction was stirred for 7 hours. The reaction mixture was partitioned between isopropyl acetate and pH 4 buffer. The layers were separated and the organic washed twice with water. The organic was dried over magnesium sulfate, filtered and concentrated. Silica gel chromatography afforded 2-methyl-2-(3-chloro-4-(3-(3-phenyl-7-propyl-6-benz[4,5] isoxazole)oxypropyl)thio)phenyl propionic acid methyl ester.

NMR (CDCl₃): 7.92 (dd, 2H, J = 7.8, 2.6 Hz); 7.63 (d, 1H, J = 8.8 Hz); 7.55-7.48 (mult, 4H); 7.39 (d, 1H, J = 2.1 Hz); 7.28 (d, 1H, J = 8.4 Hz); 7.23 (dd, 1H, J = 8.7, 2.1 Hz); 6.95 (d, 1H, J = 8.6 Hz); 4.20 (t, 2H, J = 5.7 Hz); 3.18 (t, 2H, J = 7.1 Hz); 2.92 (bt, 2H, J = 7.5 Hz); 0.96 (t, 3H, J = 7.4 Hz).

4. 2-methyl-2-(3-chloro-4-(3-(3-phenyl-7-propylbenz[4,5]isoxazol-6-oxy)propyl)thio)phenyl propionic acid

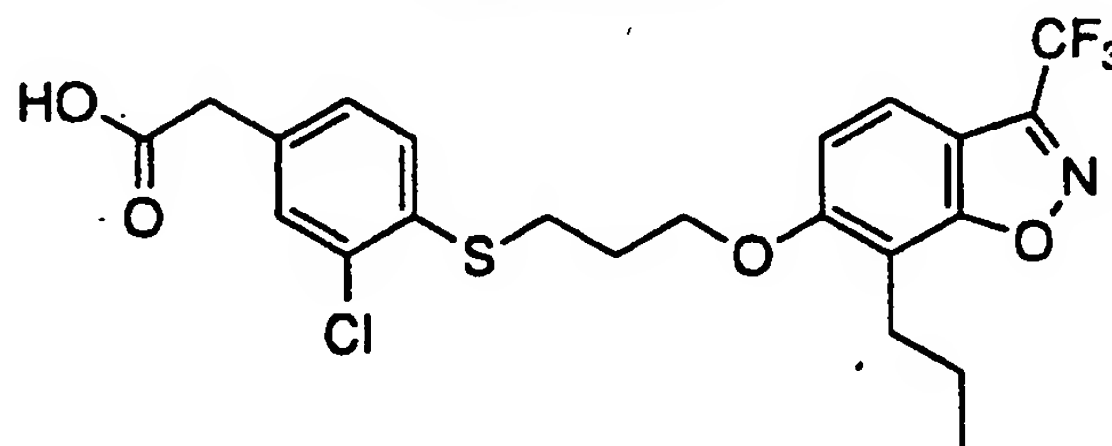
A solution of 2-methyl-2-(3-chloro-4-(3-(3-phenyl-7-propylbenz[4,5]isoxazol-6-oxy)propyl)thio)phenyl propionic acid methyl ester (0.038 grams; 0.071 mmol) in isopropanol (1 mL) was refluxed. A solution of potassium hydroxide (1.00 M; 0.212 mL; 0.212 mmol) in water was added dropwise and refluxing continued for

- 70 -

4 hours. The reaction mixture was partitioned between isopropyl acetate and 0.1N HCl. The layers were separated and the organic was dried over magnesium sulfate, filtered and concentrated. Trituration with cyclohexane/methylene chloride (3:1) afforded 2-methyl-2-(3-chloro-4-(3-(3-phenyl-7-propyl-6-benz[4,5]isoxazole) oxypropyl)thio)phenyl propionic acid

NMR (CDCl₃): 7.91 (dd, 2H, J = 7.8, 2.6 Hz); 7.63 (d, 1H, J = 8.8 Hz); 7.53-7.47 (mult, 4H); 7.40 (d, 1H, J = 2.1 Hz); 7.28 (d, 1H, J = 8.4 Hz); 7.21 (dd, 1H, J = 8.7, 2.1 Hz); 6.95 (d, 1H, J = 8.6 Hz); 3.63 (s, 3H); 4.21 (t, 2H, J = 5.7 Hz); 3.18 (t, 2H, J = 7.1 Hz); 2.90 (bt, 2H, J = 7.5 Hz); 0.98 (t, 3H, J = 7.4 Hz).

Example 20



3-chloro-4-(3-(2-propyl-3-trifluoromethyl-6-benz-[4,5]-isoxazoloxy)propylthio)phenylacetic acid

Step A: Preparation of 2,4-dihydroxy-3-propyl-trifluoroacetophenone

A solution of 2-propylresorcinol (5.0 grams) and trifluoroacetic anhydride (9.6 mL) in 1,2-dichloroethane (30.0 mL) was treated with aluminum chloride (4.38 grams). This mixture was stirred overnight. The reaction mixture was partitioned between methylene chloride and water. The organic phase was dried over sodium sulfate and filtered. The solvent was evaporated and the resulting solid was recrystallized using methylene chloride and cyclohexane (1:1) to give the titled compound.

NMR (CDCl₃) δ 7.59 (d, 1H), 6.24 (d, 1H), 5.92 (s, 1H), 2.63 (t, 2H), 1.74 (s, 1H), 1.58 (m, 2H), 0.98 (t, 3H).

- 71 -

STEP B: Preparation of 3-trifluoromethyl-7-propyl-6-hydroxy-benzisoxazole

A mixture of 2,4-dihydroxy-3-propyl-trifluoroacetophenone (2.5 grams), sodium acetate (4.18 grams), hydroxylamine hydrochloride (3.59 grams) and methanol (80 mL) was refluxed overnight. The solvent was then evaporated and the resulting solid was partitioned in ethyl acetate and pH 7 buffer. The organic phase was separated and washed with brine. The organic phase was dried over sodium sulfate and the solvent was evaporated to give a oil. The oil was then dissolved in acetic anhydride. The solution was stirred for two hours, then the acetic anhydride was evaporated in vacuo. The residue was partitioned between ethyl acetate and pH 7 buffer and the organic phase was dried over sodium sulfate. The organic phase was evaporated to give an oil. This was dissolved in pyridine and refluxed overnight. The solvent was evaporated in vacuo to give an oil which was chromatographed on silica gel using ethyl acetate and hexane (1:4) to give the titled compound.

NMR (CDCl₃) δ 7.46 (d, 1H), 6.92 (d, 1H), 5.42 (bs, 1H), 2.89 (t, 2H), 1.74 (m, 2H), 0.98 (t, 3H).

STEP C: Preparation of methyl 3-chloro-4-(3-(7-propyl-3-trifluoromethyl-6-benz- [4,5]-isoxazoloxy)propylthio)phenylacetic acid

A solution of 3-trifluoromethyl-7-propyl-6-hydroxy-benzisoxazole (2.5 grams) in 2-butanone (30 mL) was treated with 1,3-dibromopropane (4.8 mL) and potassium carbonate (5.0 grams). The mixture was refluxed for 4 hours. The reaction mixture was partitioned between isopropyl acetate and pH 4 buffer. The organic was washed once with water, then dried over magnesium sulfate. The organic was filtered and evaporated to an oil which was filtered through a silica gel plug using methylene chloride and hexane (1:2) to give 3-trifluoromethyl-7-propyl-6-(3-bromopropoxy)-benzisoxazole. A solution of 3-chloro-4-dimethylcarbamoylthio-phenylacetic acid methyl

- 72 -

ester (0.33 grams) in dry methanol (3.5 mL) was treated with a solution of sodium methoxide in methanol (25wt%; 0.341mL). The solution was refluxed for 2 hours. HPLC analysis showed the disappearance of the carbamate. The solution was allowed to cool to 50°C. 3-trifluoromethyl-7-propyl-6-(3-bromopropoxy)-benzisoxazole (0.31 grams) was added and the solution stirred for 1 hour. The reaction was partitioned between isopropyl acetate and pH 4 buffer. The organic was washed once more with pH 4 buffer, then water. The organic was dried over magnesium sulfate, filtered and concentrated to an oil. The oil was applied to a silica gel column packed with hexane/methylene chloride (2:1). The column was eluted with this mobile phase until the product began to appear in the eluant. The mobile phase was switched to 100% methylene chloride and elution continued until all the product was recovered.

NMR (CDCl₃) δ 7.52 (d, 2H), 7.30 (d, 1H), 7.27 (d, 1H), 7.12 (d, 1H), 7.08 (d, 1H), 4.21 (t, 2H), 3.68 (s, 3H), 3.54 (s, 2H), 3.15 (t, 2H), 2.89 (t, 2H), 2.19 (m, 2H), 1.68 (m, 2H), 0.94 (t, 3H).

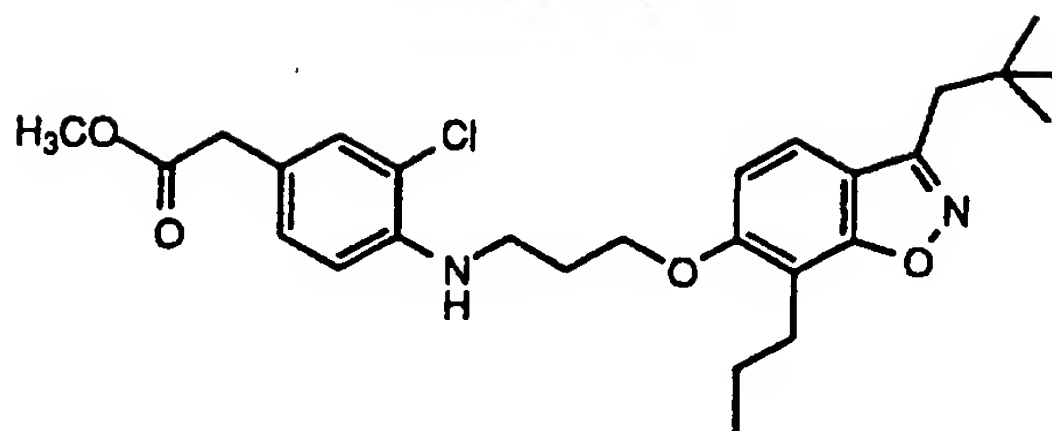
Step D: Preparation of 3-chloro-4-(3-(2-propyl-3-trifluoromethyl-6-benz-[4,5]-isoxazoloxy)propylthio)phenylacetic acid

A solution of methyl 3-chloro-4-(3-(2-propyl-3-trifluoromethyl-6-benz-[4,5]-isoxazoloxy)propylthio)phenylacetic acid (0.113 grams) in methanol (1.5 mL) was treated with a solution of lithium hydroxide in water (1.01 M; 0.362 mL). The reaction was refluxed 1 hour. The reaction mixture was partitioned between isopropyl acetate and 0.1N HCl. The organic was dried over magnesium sulfate, filtered and concentrated to a solid. The solid was suspended in methylene chloride/cyclohexane (1:1; 2 mL). The mixture was refluxed briefly and cooled to 0°C. The title compound was isolated by filtration.

NMR (CDCl₃) δ 7.53(d, 2H), 7.31 (d, 1H), 7.27 (d, 1H), 7.12 (d, 1H), 7.02 (d, 1H), 4.21 (t, 2H), 3.57 (s, 2H), 3.16 (t, 2H), 2.89 (t, 2H), 2.19 (m, 2H), 1.67 (m, 2H), 0.93 (t, 3H).

ESI-MS: m/e = 488 (m+1).

- 73 -

Example 21

Methyl 3-chloro-4-(3-(3-(2,2-dimethylpropyl)-7-propyl-6-benz-[4,5]-isoxazoloxy)-propylamino)phenylacetate

Step A: Preparation of 3-chloro-4-acetamidophenylacetic acid

Acetic anhydride (152 mL, 1.6 moles) was added dropwise to a rapidly stirring mixture of 4-aminophenylacetic acid (195 grams, 1.3 moles) in acetic acid (600 mL) and water (250 mL) at room temperature. After a slight exotherm, the dark brown solution was stirred for one hour at room temperature. The solution was diluted with ethanol (500 mL) and water (250 mL), and a suspension of Calcium hypochlorite (340 grams, 2.3 moles) in water (1 L plus 500mL rinse) was added portionwise. The temperature rose to 50°C and the mixture was stirred for 16 hours at room temperature. The mixture was poured into ice-water (8 L) and extracted with ethyl acetate (3x 2L). The combined extracts were washed with saturated brine, dried over magnesium sulfate and concentrated *in vacuo* to a small volume. Hexane was added and the resulting precipitate filtered, washed with hexane and dried to give the title compound (180 grams) as a brown solid.

NMR (CDCl₃ + 10% CD₃OD): δ 2.12 (s, 3H); 3.45 (s, 2H); 7.10 (dd, 2H); 8.02 (dd, 1H).

Step B: Preparation of methyl 3-chloro-4-aminophenylacetate·HCl

A solution of 3-chloro-4-acetamidophenylacetic acid (180 grams, 0.79 moles) in methanol (2 L), was treated with concentrated HCl (200 mL) and the resulting solution refluxed for 6 hours and then stirred at room temperature for 16 hours. The mixture was

- 74 -

concentrated *in vacuo* to about one-half its volume and ether (4 L) was added. The resulting precipitate was filtered, washed with ether and dried to give the title compound (173 grams) as a tan solid NMR, (CD₃OD): δ 3.70 (s, 2H); 3.73 (s, 3H); 7.35 (d, 1H); 7.43 (d, 1H); 7.56 (s, 1H).

Step C: Preparation of methyl 3-chloro-4-(3-bromopropylamino)phenylacetate

Magnesium oxide (10 grams, 250 mmoles), was added to a solution of 1,3-dibromopropane (139 grams, 70 mL, 700 mmoles) in dimethylacetamide (150 mL). A solution of methyl 3-chloro-4-aminophenylacetate·HCl (23.6 grams, 100 mmoles) in dimethylacetamide (200 mL) was added dropwise over 30 minutes and the mixture stirred at 80°C for 6 hours. The cooled mixture was partitioned with methylene chloride and water. The aqueous phase was extracted with methylene chloride and the combined organic phases washed with brine, dried over magnesium sulfate and concentrated *in vacuo* to an oil. The crude product was chromatographed on a silica gel column eluting with hexane:ethyl acetate (9:1). The product was further purified by a second silica gel chromatography in methylene chloride:hexane (2:3) to give the title compound as an oil. NMR, (CDCl₃): δ 2.15 (qnt, 2H); 3.35 (q, 2H); 3.47 (s, 2H); 3.49 (t, 2H); 3.67 (s, 3H); 6.63 (d, 1H); 7.03 (dd, 1H); 7.17 (d, 1H).

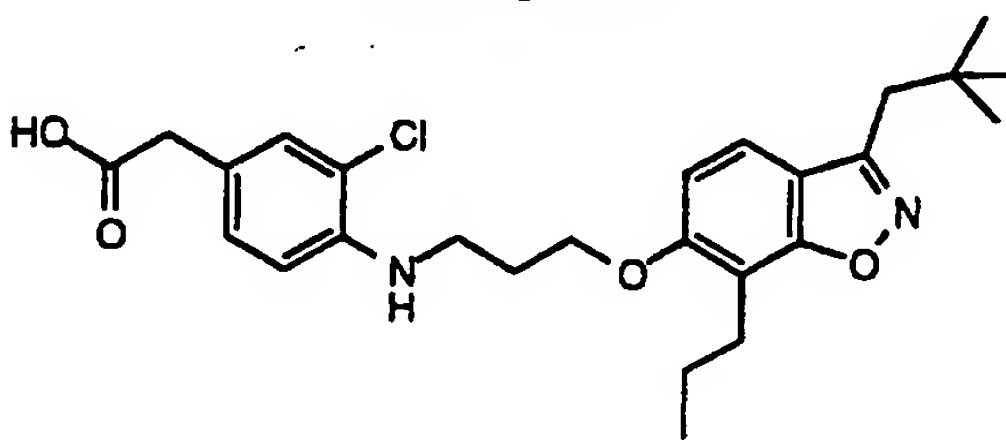
Step D: Preparation of 3-chloro-4-(3-(3-(2,2-dimethylpropyl)-7-propyl-6-benz-[4,5]-isoxazoloxy)-propylamino)phenylacetate

A solution of methyl 3-chloro-4-(3-bromopropylamino)phenylacetate (4.55 grams, 14.19 mmoles) and 3-(2,2-dimethylpropyl)-6-hydroxy-7-propylbenz-[4,5]-isoxazole (3.51 grams, 14.19 mmoles) in 2-butanone (50 mL) was treated with potassium carbonate (2.35 grams, 17.0 mmoles). The mixture was refluxed for 8 hours, stirred at room temperature for 16 hours and filtered. Evaporation *in vacuo* followed by flash chromatography on silica gel in hexane:ethyl acetate (9:1)

- 75 -

afforded the title compound as a white solid. NMR, (CD₃OD): δ 0.94 (t, 3H); 1.04 (s, 9H); 1.70 (m, 2H); 2.15 (m, 2H); 2.83 (s, 2H); 2.90 (t, 2H); 3.45 (t, 2H); 3.48 (s, 2H); 3.66 (s, 3H); 4.22 (t, 2H); 6.71 (d, 1H); 6.99 (d, 1H); 7.07 (d, 1H); 7.15 (d, 1H); 7.52 (d, 1H).

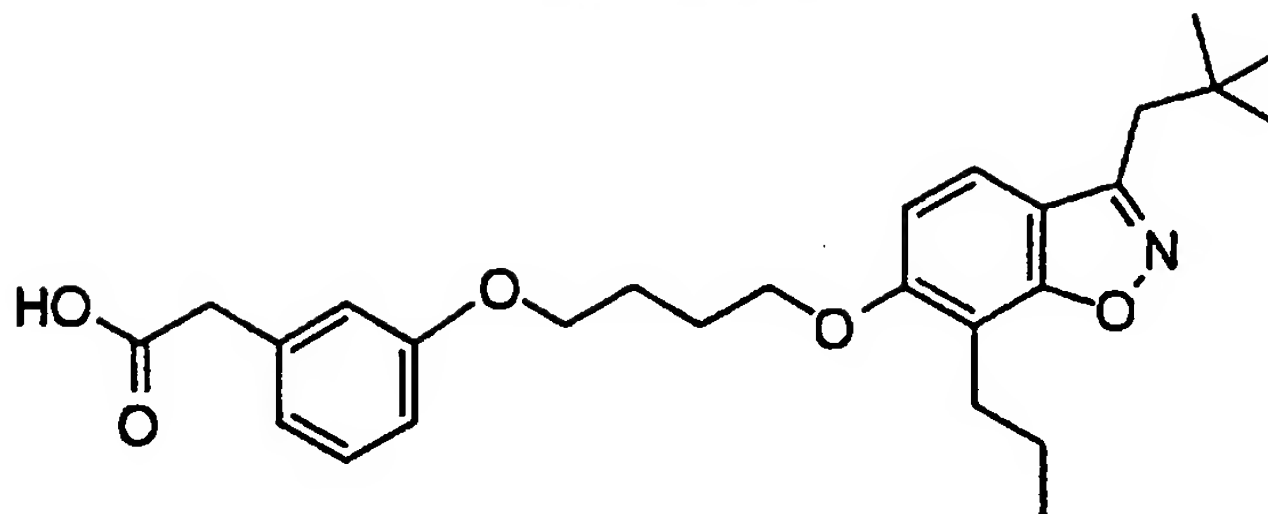
Example 22



3-Chloro-4-(3-(3-(2,2-dimethylpropyl)-7-propyl-6-benz-[4,5]-isoxazoloxy)-propylamino)phenylacetic acid

To a solution of methyl 3-chloro-4-(3-(3-(2,2-dimethylpropyl)-7-propyl-6-benz-[4,5]-isoxazoloxy)-propylamino)phenylacetate (4.24 grams, 8.71 mmol) in methanol (90 mL) was added a solution of lithium hydroxide (1M, 17.42 mL, 17.42 mmol), and the resulting mixture stirred at 60°C for 2.5 hours. The solution was evaporated *in vacuo* and the residue diluted with water and ethyl acetate. The pH was brought to 5.0 with 1M hydrochloric acid and organic phase separated. The aqueous phase was extracted 3 times with ethyl acetate and the combined organic extracts dried over magnesium sulfate and evaporated *in vacuo* to give the title compound as a white crystalline solid. (mp = 115-116°C.; Mass spec = 473, 475, calc = 473) NMR, (CD₃OD): δ 0.96 (t, 3H); 1.03 (s, 9H); 1.71 (m, 2H); 2.15 (m, 2H); 2.83 (s, 2H); 2.90 (t, 2H); 3.44 (s, 2H); 3.45 (t, 2H); 4.22 (t, 2H); 6.72 (d, 1H); 7.01 (d, 1H); 7.03 (d, 1H); 7.07 (d, 1H); 7.16 (d, 1H); 7.50 (d, 1H).

- 76 -

Example 23

3-(4-(3-(2,2-dimethylpropyl)-7-propyl-6-benz-[4,5]-isoxazoloxy)-butoxy)phenylacetic acid

Step 1A

A solution of 2,4-dihydroxy-3-propylphenyl ethyl ketone (25.545 grams) in 2-butanone (300 mL) was treated with 1,3-dibromopropane (48.79 mL) and potassium carbonate (50.859 grams). The mixture was refluxed for 4 hours. The reaction mixture was partitioned between isopropyl acetate and pH 4 buffer. The organic was washed once with water, then dried over magnesium sulfate. The organic was filtered and evaporated to an oil which was chromatographed over silica gel with hexane/methylene chloride (2:1) to afford the title compound.

Step 1

The ester was obtained from the Fischer esterification of the commercially available acid in methanol. The 3-hydroxyphenylacetic acid (25g) was dissolved in methanol (100 ml) with approximately 0.4 ml H₂SO₄ conc. The mixture was heated 16 Hrs under reflux. The mixture was cooled and reduced *i. vac.* The residue was taken up in ethyl acetate and washed with sat'd aq NaHCO₃, followed by sat'd aq NaCl. The EtOAc extracts were dried over MgSO₄ and reduced *i. vac.* The ester was used without further purification. Characteristic NMR Resonances; ¹H NMR 400MHz (CDCl₃); 7.15 (t, 1H, J=7.7 Hz), 6.80 (t, 1H, J=8.1 Hz), 6.75 (brd s, 1H), 6.72 (dd, 1H, J=2.6, 8.1 Hz), 3.68 (s, 3H), 3.56 (s, 2H).

- 77 -

Step 2

The ester (4.0 g, 1 Eq, 0.024 mol) was dissolved in DMF (30 ml) with 1,4-dibromobutane (14.4 ml, 5 Eq, 0.121 mol) and CsCO_3 (8.3 g, 1.05 Eq, 0.025 mol). The suspension was stirred 1.5 Hrs at RT. The mixture was poured into 0.2 N HCl and EtOAc. The aqueous phase was extracted with EtOAc and the EtOAc extracts washed three times with water, followed by sat'd aq NaCl. The extracts were dried over MgSO_4 and reduced *i. vac.*

The product was purified by elution from a silica gel column (150 g E. Merck 40-63 μ) with 9 : 1 Hexanes : EtOAc. The bromide is obtained as an oil.

Characteristic NMR Resonances; ^1H NMR 400MHz (CDCl_3); 7.21 (t, 1H, $J=7.9$ Hz), 6.86-6.76 (m, 3H), 3.97 (t, 2H, $J=6.0$ Hz), 3.67 (s, 3H), 3.58 (s, 2H), 3.47 (t, 2H, $J=6.6$ Hz), 2.02-2.09 (complex m, 2H), 1.89-1.96 (complex m, 2H).

Step 3

The hydroxybenzisoxazole (41 mg, 1.0 Eq, 0.165 mmol) was dissolved in DMF (0.5 ml) with the bromide (52 mg, 1.05 Eq, 0.174 mmol) and CsCO_3 (59 mg, 1.1 Eq, 0.182 mmol). The suspension was stirred 16 Hrs at RT. The mixture was poured into 0.2 N HCl and EtOAc. The aqueous phase was extracted with EtOAc and the EtOAc extracts washed with sat'd aq NaCl. The extracts were dried over Na_2SO_4 and reduced *i. vac.* The product was purified by elution from a silica gel column (10 g E. Merck 40-63 μ) with 98 : 2 toluene : EtOAc. The product is obtained as an oil.

Characteristic NMR Resonances; ^1H NMR 400MHz (CDCl_3); 7.34 (d, 1H, $J=8.7$ Hz), 7.21 (t, 1H, $J=7.9$ Hz), 6.88 (d, 1H, $J=8.7$ Hz), 6.85-6.78 (m, 3H), 4.11 (t, 2H, $J=5.7$ Hz), 4.03 (t, 2H, $J=5.7$ Hz), 3.67 (s, 3H), 3.57 (s, 2H), 2.86 (dd, 2H, $J=8.9, 7.5$ Hz), 2.79 (s, 2H), 1.99 (m, 4H), 1.69 (sext, 2H, $J=7.5$ Hz), 1.03 (s, 9H), 0.95 (t, 3H, $J=7.4$ Hz).

MS ESI CH_3CN / NH_4CO_2 aq. $M+1$ 468.5.

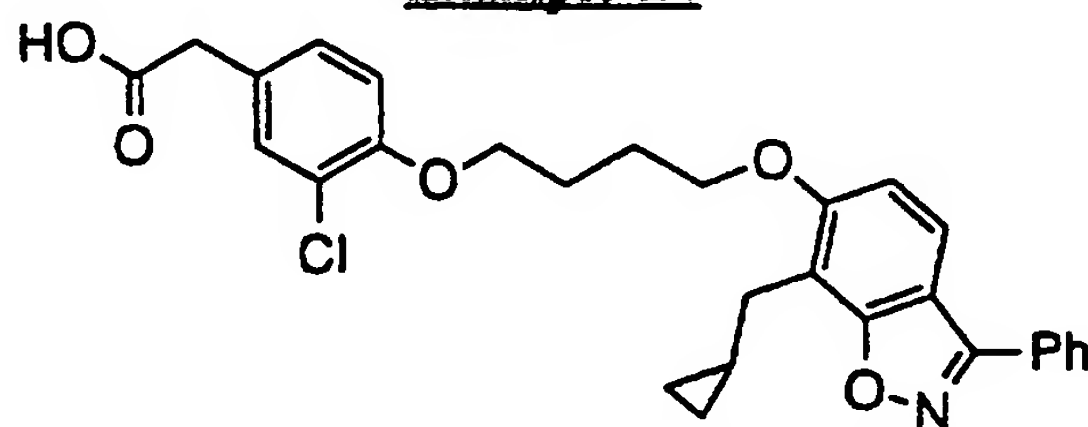
- 78 -

Step 4

The ester (60 mg, 1 Eq, 0.13 mmol) was dissolved in approximately 3 ml 2 : 1 dioxane : H₂O. 1.5 M Aqueous LiOH (170 ml, 2.0 Eq, 0.25 mmol) was added dropwise at RT and the mixture stirred 1 Hr. The reaction mixture was diluted into 0.2 N HCl and EtOAc. The aqueous phase was extracted with EtOAc and the EtOAc extracts washed with sat'd aq NaCl. The extracts were dried over Na₂SO₄ and reduced *i. vac.* The product is obtained as an oil.

Characteristic NMR Resonances; ¹H NMR 400MHz (CDCl₃); 7.34 (d, 1H, J=8.6 Hz), 7.24 (t, 1H, J=7.7 Hz), 6.88 (d, 1H, J=8.7 Hz), 6.85-6.79 (m, 3H), 4.10 (t, 2H, J=5.7 Hz), 4.03 (t, 2H, J=5.7 Hz), 3.59 (s, 2H), 2.85 (dd, 2H, J=8.9, 7.5 Hz), 2.79 (s, 2H), 1.99 (m, 4H), 1.67 (sext, 2H, J=7.5), 0.94 (t, 3H, J=7.4 Hz).

MS ESI CH₃CN / NH₄CO₂ aq. M+1 454.5.

Example 24

3-chloro-4-(3-(3-phenyl-7-cyclopropylmethyl-6-benz-[4,5]-isoxazoloxy)-butyloxy)phenylacetic acid

Step A: Preparation of 7-cyclopropylmethyl-3-phenyl-6-hydroxybenz-[4,5]-isoxazole

A solution of 2,4-dihydrobezophenone (2.14 grams) in DMF (20 mL) was treated with potassium carbonate (1.45 grams). This mixture was heated to 40°C and stirred for 0.5 hours. To this mixture was added allyl bromide (3.6 grams), then the reaction was stirred overnight. The mixture was diluted with ethyl acetate and washed with 1 M HCl solution and brine. The organic phase was dried over sodium sulfate and filtered. The solvent was removed in vacuo and the resulting oil was filtered through a plug of silica gel using methylene chloride and

- 79 -

hexane (1:2) to give 4-allyloxy-2-hydroxybenzophenone. This was then dissolved in 1,2-dichlorobenzene and refluxed for 24 hours. The solvent was evaporated in vacuo and the resulting oil was filtered through a plug of silica gel using methylene chloride and hexane (1:1) to give 3-allyl-2,4-dihydrobezophenone. 3-allyl-2,4-dihydrobezophenone (1.0 grams) was dissolved in methanol (20 mL) and treated with hydroxylamine hydrochloride (1.35 grams) and sodium acetate (1.6 grams) and refluxed overnight. The solvent was evaporated in vacuo and the resulting solid was partitioned in ethyl acetate and pH 7 buffer. The organic phase was dried over sodium sulfate and filtered. The solvent was removed to give a solid. This was stirred in acetic anhydride for 2 hours; and then the solvent was removed in vacuo to give an oil. The oil was dissolved in pyridine and refluxed overnight. The solvent was evaporated in vacuo and the residue was filtered through a pad of silica gel using methylene chloride and hexane (1:1) to give 7-allyl-3-phenyl-6-hydroxybenz-[4,5]-isoxazole. To a solution of 7-allyl-3-phenyl-6-hydroxybenz-[4,5]-isoxazole (0.5 grams) in 2 mL of ethyl ether was added diazomethane (15 mL of a 0.70M soln. in Et₂O) under nitrogen followed by the addition of palladium acetate (cat., 2 mg). The reaction mixture was stirred at ambient temperature for 30 min until gas evolution had ceased. The ether was evaporated *in vacuo*, and the residue was purified on a silica gel flash chromatography column eluted with 10% EtOAc:hexane. Evaporation of the purified fractions and solvent removal *in vacuo* afforded the product.

NMR (CDCl₃) δ 7.91 (d, 2H), 7.58 (d, 1H), 7.53 (m, 3H), 6.89 (d, 1H), 5.64 (s, 1H), 2.91 (d, 2H), 1.24 (m, 1H), 0.54 (m, 2H), 0.37 (d, 2H).

STEP B: Preparation of 3-chloro-4-(3-(3-phenyl-7-cyclopropylmethyl-6-benz-[4,5]-isoxazoloxy)-butyloxy)phenylacetic acid

A solution of 7-cyclopropylmethyl-3-phenyl-6-hydroxybenz-[4,5]-isoxazole (0.25 grams) in 2-butanone (3.0 mL) was treated with 1,3-dibromopropane (0.48 mL) and potassium carbonate (0.50 grams). The mixture was refluxed for 4 hours. The reaction

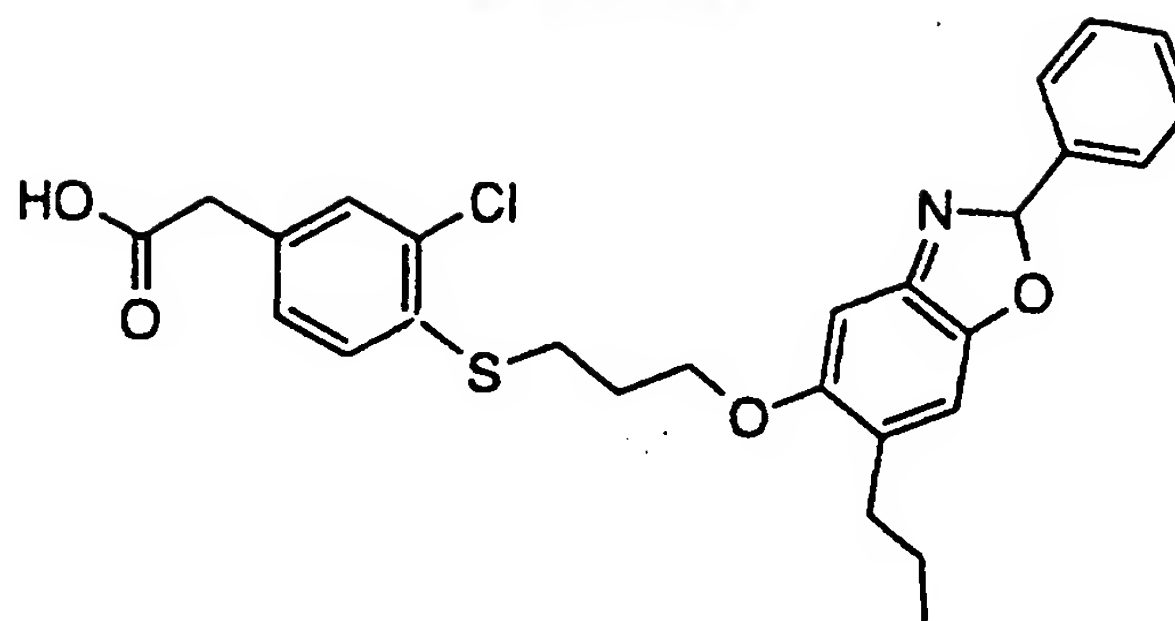
- 80 -

mixture was partitioned between isopropyl acetate and pH 4 buffer. The organic was washed once with water, then dried over magnesium sulfate. The organic was filtered and evaporated to an oil which was filtered through a silica gel plug using methylene chloride and hexane (1:2) to give 7-cyclopropylmethyl-3-phenyl-6-(3-bromopropoxy)benz-[4,5]-isoxazole. A solution of 3-chloro-4-hydroxyphenylacetic acid methyl ester (42.0 mg) in DMF (1.0 mL) was treated with potassium carbonate (26 mg) and this mixture was stirred for 0.5 hours. Then 7-cyclopropylmethyl-3-phenyl-6-(3-bromopropoxy)benz-[4,5]-isoxazole was added and the mixture was stirred over night. The reaction mixture was partitioned between ethyl acetate and 1 M HCl solution. The organic was dried over sodium sulfate and filtered. The solvent was removed in vacuo and the residue was chromatographed on silica gel using methylene chloride and hexane (1:1) to give an oil. A solution of methyl 3-chloro-4-(3-(3-phenyl-7-cyclopropylmethyl-6-benz-[4,5]-isoxazoloxo)-butyloxy)phenylacetic acid (0.04 grams) in methanol (1.5 mL) was treated with a solution of lithium hydroxide in water (1.01 M; 0.1 mL). The reaction was refluxed 1 hour. The reaction mixture was partitioned between isopropyl acetate and 0.1N HCl. The organic was dried over magnesium sulfate, filtered and concentrated to a solid. The solid was suspended in methylene chloride/cyclohexane (1:1; 2 mL). The mixture was refluxed briefly and cooled to 0°C. The title compound was isolated by filtration.

NMR (CDCl₃) δ 7.93(d, 2H), 7.65 (d, 1H), 7.53 (m, 3H), 7.28 (s, 1H), 7.01 (d, 1H), 6.98 (d, 1H), 6.87 (d, 1H), 4.18 (t, 2H), 4.08 (t, 2H), 3.55 (s, 2H), 2.88 (d, 2H), 2.08 (m, 4H), 0.41 (m, 2H), 0.30 (m, 2H).

ESI-MS: m/e = 506 (m+1).

- 81 -

Example 25

3-chloro-4-(3-(2-phenyl-6-propyl-5-benz-[4,7]-oxazoloxo)propylthio)phenylacetic acid

Step A: Preparation of 1-propenyloxy-4-benzyloxy benzene:

5.0 grams (25.0 mmole, 1.0 eq.) of 4-benzyloxyphenol was dissolved in 100 ml of N,N-dimethylformamide. 10.4 grams (75.0 mmole, 3.0 eq.) of potassium carbonate and 3.25 ml (37.5 mmole, 1.5 eq.) of allyl bromide were added to the reaction and it was stirred at 80°C for 3 hours and at room temperature for another 136 hours. The reaction mixture was diluted with water and extracted 3x with 60 ml of ethyl acetate. The combined organics were dried over sodium sulfate, filtered, evaporated and pumped on high vacuum overnight. The title compound (4.3 grams, 72% yield) was isolated by recrystallization from methanol.

NMR (400 MHz, CDCl₃) δ 7.36 (m, 5H), 6.88 (m, 4H), 6.04 (m, 1H), 5.39 (d, 1H), 5.24 (d, 1H), 5.01 (s, 2H), 4.44 (d, 2H).

Step B: Preparation of 2-propenyl-4-benzyloxyphenol:

7.5 grams (31.3 mmole, 1.0 eq.) of product from step A was dissolved in 35 ml of 1,2-dichloroethane and heated to reflux for 24 hours. The reaction mixture was directly chromatographed after cooling to give 6.8 grams (91% yield) of the title compound.

NMR (300MHz, CDCl₃) δ 7.36 (m, 5H), 6.77 (d, 1H), 6.74 (m, 2H), 6.00 (m, 1H), 5.18 (dm, 2H), 4.99 (s, 2H), 4.58 (s, 1H), 3.39 (dd, 2H).

- 82 -

Step C **Preparation of 2-propylhydroquinone:**

6.8 grams (28.4 mmole, 1.0 eq.) of product from step B was dissolved in 60 ml of methanol. 680 mg of 10% palladium on carbon (0.64 mmole, 0.023 eq.) was added and the stirring suspension was evacuated and charged with hydrogen. After 16 hours the catalyst was filtered over celite and the filtrate evaporated. The title compound (4.3 grams) was recovered by recrystallization from dichloromethane/hexanes.

NMR (400 MHz, CD₃OD) δ 6.56 (d, 1H), 6.51 (d, 1H), 6.43 (dd, 1H), 2.48 (t, 2H), 1.58 (m, 2H), 0.96 (t, 3H).

Step D: **Preparation of 1,4-dimethoxy-2-propyl benzene:**

1.0 gram (6.6 mmole, 1.0 eq.) of product from step C was dissolved in 30 ml of freshly distilled THF. The solution was cooled to 0°C and 0.65 gram of 61% sodium hydride (16.5 mmole, 2.5 eq) and 1.25 ml (20.1 mmole, 3.0 eq.) of iodomethane were added. The reaction was stirred at 0°C for 16 hours under nitrogen atmosphere. The reaction was quenched with saturated aqueous ammonium chloride and extracted 3x with dichloromethane. The organic was dried over sodium sulfate, filtered and evaporated. The recovered crude material was chromatographed to give 0.96 gram of the title compound as a clear liquid.

NMR (400 MHz, CDCl₃) δ 6.74 (d, 1H), 6.71 (d, 1H), 6.66 (dd, 1H), 3.76 (s, 3H), 3.74 (s, 3H), 2.55 (t, 2H), 1.60 (m, 2H), 0.96 (t, 3H).

Step E: **Preparation of 2,5-dimethoxy-4-propyl benzophenone:**

0.254 gram (1.4 mmole, 1.0 eq.) of product from step D was dissolved in 7 ml of 1,2-dichloroethane, after which 0.20 ml of benzoyl chloride and 0.225 gram aluminum (III) chloride (1.7 mmole, 1.2 eq. each) were added. Stirred at room temperature under nitrogen atmosphere for 75 minutes, then quenched with aqueous potassium carbonate. Diluted further with water and extracted 3x with dichloromethane. The combined organics were dried over sodium

- 83 -

sulfate, filtered and evaporated. The resulting crude material was chromatographed to give 0.38 gram (95% yield) of the title compound. NMR (400 MHz, CDCl_3) δ 7.80 (dd, 2H), 7.53 (dt, 1H), 7.42 (t, 2H), 6.88 (s, 1H), 6.78 (s, 1H), 3.77 (s, 3H), 3.62 (s, 3H), 2.62 (t, 2H), 1.64 (m, 2H), 0.97 (t, 3H).

Step F: Preparation of 2,5-dihydroxy-4-propyl benzophenone:

0.37 gram (1.3 mmole, 1.0 eq.) of product from step E was dissolved in 5 ml of dichloromethane. The solution was stirred under nitrogen atmosphere at -78°C and 3.2 ml of 1.0 M boron tribromide solution in hexanes (3.2 mmole, 2.5 eq.) was added dropwise over a 5-8 minute span. The reaction was allowed to slowly warm, and after 3 hours ice was added to the reaction mixture. After an additional 30 minutes some water was added and the mixture was diluted with dichloromethane. The layers were separated and the organic was washed twice more with water, dried over sodium sulfate, filtered and evaporated to give the title compound (0.33 gram, 100% yield) without further purification.

NMR (400 MHz, CDCl_3) δ 11.65 (s, 1H), 7.65 (dd, 2H), 7.55 (dt, 1H), 7.46 (t, 2H), 6.92 (s, 1H), 6.84 (s, 1H), 4.34 (s, 1H), 2.59 (t, 2H), 1.67 (m, 2H), 0.98 (t, 3H).

Step G: Preparation of 2,5-dihydroxy-4-propyl benzoxime:

0.22 gram (0.88 mmole, 1.0 eq.) of product from step F was dissolved in 2.5 ml of 100% ethanol. 0.61 gram of hydroxylamine hydrochloride and 0.72 gram of sodium acetate (8.8 mmole, 10 eq. each) were then added and the reaction was heated to reflux under nitrogen atmosphere for 16 hours. The reaction was cooled to room temperature and diluted with water and ethyl acetate. The layers were separated and the organic layer was washed twice more with water, then dried over sodium sulfate, filtered and evaporated to give 0.23 gram (97% yield) of the title compound without further purification.

- 84 -

NMR (400 MHz, CDCl_3) δ 7.40 (m, 5H), 6.88 (s, 0.25H), 6.78 (s, 0.75H), 6.37 (s, 0.25H), 6.19 (s, 0.75H), 2.58 (t, 0.5H), 2.50 (t, 1.5H), 1.62 (m, 2H), 0.99 (t, 0.75H), 0.98 (t, 2.25H).

Step H: Preparation of 2-phenyl-5-hydroxy-6-propyl benz-[4,7]-oxazole:

0.23 gram (0.83 mmole, 1.0 eq.) of product from step G was dissolved in 0.75 ml of acetonitrile and 0.25 ml of N,N-dimethylacetamide. Under a nitrogen atmosphere 0.085 ml (0.91 mmole, 1.1 eq.) of phosphorus oxychloride was added and the reaction stirred for 30 minutes. Water and ethyl acetate were added, as was solid sodium acetate (ca. 0.3 gram). The layers were separated and the organic was washed with saturated aqueous sodium chloride solution, then dried over sodium sulfate, filtered and evaporated. The crude was purified by column chromatography to give 0.12 gram (57% yield) of the title compound. Structure confirmed by NMR, MS, and NOE difference spectroscopy.

NMR (500 MHz, $\text{DMSO}-d_6$) δ 9.39 (s, 1H), 8.11 (m, 2H), 7.56 (m, 3H), 7.42 (s, 1H), 7.10 (s, 1H), 2.62 (t, 2H), 1.61 (m, 2H), 0.91 (t, 3H). MS[ESI]: m/e 254.1 (M+1).

Step I: Preparation of methyl 3-chloro-4-(3-bromopropylthio)phenyl acetate:

10.0 grams (34.7 mmole, 1.0 eq.) of 3-chloro-4-dimethylcarbamoylthio-phenylacetic acid methyl ester was dissolved in 15 ml anhydrous methanol, then 8.3 ml of 25% w/w (38.2 mmole, 1.1 eq.) sodium methoxide in methanol was added and the reaction heated to reflux for one hour. In a separate flask, 14.1 ml (139 mmole, 4.0 eq.) of 1,3-dibromopropane was dissolved in 15 ml of anhydrous methanol, which was then cooled by an ice bath. The sodium thiolate solution was cooled to room temperature, then added dropwise via cannula to the stirring dibromopropane. After 30 minutes at 0°C and one hour at room temperature, the reaction was quenched by adding saturated aqueous ammonium chloride followed by water. The aqueous was

- 85 -

extracted twice with ethyl acetate. The combined organics were washed with water (2x) and saturated sodium chloride (1x). The organic layer was dried over sodium sulfate, filtered and evaporated. The recovered crude material was purified by silica gel chromatography to give 8.1 gram (71% yield) of the title compound.

NMR (500 MHz, CDCl_3) δ 7.34 (d, 1H), 7.30 (d, 1H), 7.17 (dd, 1H), 3.72 (s, 3H), 3.59 (s, 2H), 3.57 (t, 2H), 3.10 (t, 2H), 2.20 (quint, 2H).

Step J Preparation of methyl 3-chloro-4-(3-(2-phenyl-6-propyl-5-benz-[4,7]-oxazoloxo) propylthio) phenyl acetate:

20.0 mg of product from step H (79 μmole , 1.0 eq.) was dissolved in 0.75 ml of N,N-dimethylformamide. 27.0 mg of cesium carbonate (83 μmole , 1.05 eq.) and 26.7 mg (79 μmole , 1.0 eq.) of product from step I were then added, and the reaction stirred at 65°C for 2 hours. The reaction mixture was diluted with water, acidified with dilute aqueous HCl and extracted with ethyl acetate. The organic was dried over sodium sulfate, filtered and evaporated, then purified by silica gel chromatography to give 26.5 mg (66% yield) of the title compound.

NMR (500 MHz, CDCl_3) δ 8.23 (m, 2H), 7.52 (m, 3H), 7.37-7.30 (m, 3H), 7.20 (s, 1H), 7.15 (dd, 1H), 4.34 (t, 2H), 3.72 (s, 3H), 3.58 (s, 2H), 3.21 (t, 2H), 2.74 (t, 2H), 2.23 (m, 2H), 1.70 (m, 2H), 1.00 (t, 3H).

Step K: Preparation of 3-chloro-4-(3-(2-phenyl-6-propyl-5-benz-[4,7]-oxazoloxo)propylthio) phenylacetic acid:

24.6 mg (48.2 μmole , 1.0 eq.) of the product from step J was dissolved in 0.6 ml of a 1:1 mixture of tetrahydrofuran and methanol. Then 0.35 ml of 0.25N lithium hydroxide (87.5 μmole , 1.8 eq.) was added and the reaction stirred for 16 hours. Then the reaction was heated to 80°C for 20 minutes, but this failed to push the reaction to completion. The reaction mixture was diluted with water, acidified with dilute HCl, and extracted with ethyl acetate. The organic was dried over sodium sulfate, filtered and evaporated. The recovered crude was purified by silica gel chromatography that utilized an acetic acid

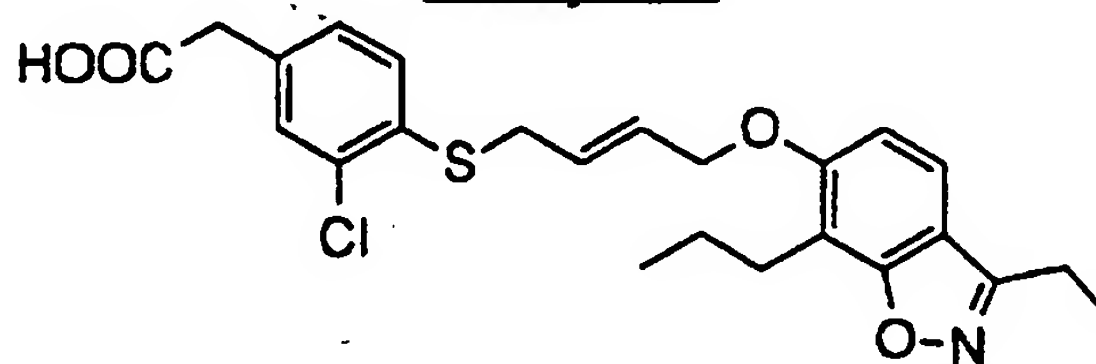
- 86 -

modified mobile phase, giving 16.4 mg (69% yield) of the title compound.

NMR (500 MHz, CDCl₃) δ 8.24 (m, 2H), 7.54 (m, 3H), 7.46 (d, 1H), 7.42 (d, 1H), 7.33 (s, 1H), 7.24 (dd, 1H), 6.81 (s, 1H), 3.85 (t, 2H), 3.64 (s, 2H), 3.23 (t, 2H), 2.70 (t, 2H), 2.29 (m, 2H), 1.66 (m, 2H), 0.97 (t, 3H).

MS[ESI]: m/e 496.2 (M+1).

Example 26



3-chloro-4-(3-(3-ethyl-7-propyl-6-benz-[4,5]-isoxazoloxy)-but-2-en-thio)phenylacetic acid

STEP A: Preparation of 1-bromo-4-(3-ethyl-7-propyl-6-benz-[4,5]-isoxazoloxy)but-2-ene

Using the method found in example 1 step A, substituting 2-hydroxy-3-ethyl-7-propyl-6-benz-[4,5]-isoxazoloxy as the starting material and substituting 1,4-dibromobut-2-ene in place of 1,3-dibromopropane, the titled compound was obtained. This compound purified by filtering it through a plug of silica gel, using 100% hexane and then 20% ethyl acetate/ hexane to remove the excess 1,4-dibromobut-2-ene.

NMR (CDCl₃) δ 7.37 (d, 1H, J = 8.7 Hz); 6.85 (d, 1H, J = 8.7 Hz); 6.03 (m, 2H); 4.63 (d, 2H, J = 5.78 Hz); 3.99 (d, 2H, J = 7.2 Hz); 2.93 (q, 2H, J = 7.65 Hz); 2.86 (t, 2H, J = 6.27 Hz); 1.67 (m, 2H); 1.40 (t, 3H, J = 7.61 Hz); 0.948 (t, 3H, J = 7.4 Hz).

STEP B: Preparation of Methyl 3-chloro-4-(4-(3-ethyl-7-propyl-6-benz-[4,5]-isoxazoloxy)-but-2-en-thio)phenylacetate

- 87 -

Using the method in example 1 step B, substituting 1-bromo-4-(3-ethyl-7-propyl-6-benz-[4,5]-isoxazoloxy)but-2-ene as the starting material, the titled compound was obtained. This compound was taken forward without further purification.

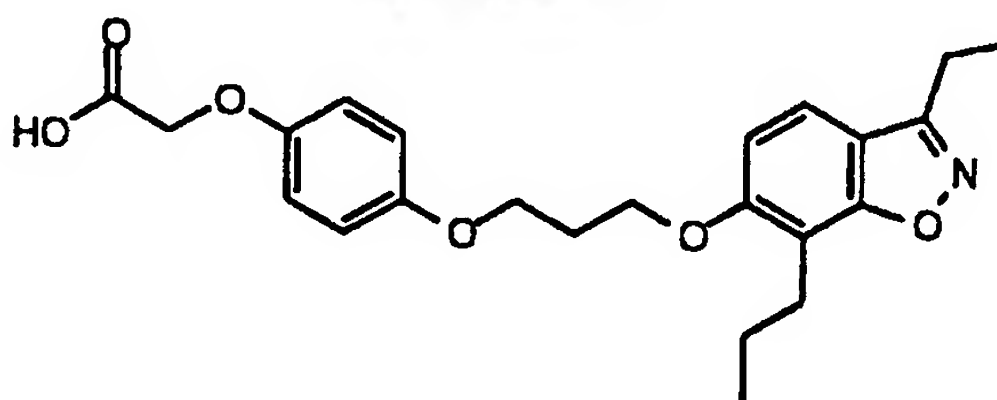
STEP C: Preparation of 3-chloro-4-(4-(3-ethyl-7-propyl-6-benz-[4,5]-isoxazoloxy)-but-2-en-thio)phenylacetic acid

Using the method in example 2 step A (19632PV2), substituting Methyl 3-chloro-4-(4-(3-ethyl-7-propyl-6-benz-[4,5]-isoxazoloxy)-but-2-en-thio)phenylacetate as the starting material, the titled compound was obtained.

NMR (CDCl₃) δ 7.33 (d, 1H, J = 8.63 Hz); 7.29 (s, 1H); 7.20 (d, 1H, J = 8.13); 7.06 (d, 1H, J = 8.09 Hz); 6.80 (d, 1H, J = 8.63 Hz); 5.87 (m, 2H); 4.55 (d, 2H, J = 4.4 Hz); 3.60 (d, 2H, J = 5.62 Hz); 3.56 (s, 2H); 2.93 (q, 2H, J = 7.6 Hz); 2.81 (t, 2H, J = 7.4 Hz); 1.64 (m, 2H, J = 7.49 Hz); 1.41 (t, 3H, J = 7.61 Hz); 0.91 (t, 3H, J = 7.41 Hz).

ESI: Mass spec: m/e = 460 (M+1).

Example 27



4-(3-(3-ethyl-7-propyl-6-benz[4,5]isoxazole)oxy)propyloxy phenoxy acetic acid

1. Methyl p-Hydroxyphenoxy acetate

A solution of p-hydroxyphenyl acetic acid (4.602 grams; 27.368 mmol) in dry methanol (80 mL) was treated with con. H₂SO₄ (0.50 mL). The solution was stirred at 55° C for 2 hours. The reaction was partitioned between isopropyl acetate and aqueous sodium

- 88 -

bicarbonate solution. The organic was dried over magnesium sulfate, filtered and evaporated to afford the title compound as a solid.

NMR (acetone): 6.75 (apparent quart, 4H, $J = 9.5$ Hz); 4.60 (s, 2H); 3.71 (s, 3H).

2. Methyl 4-(3-(3-ethyl-7-propyl-6-benz[4,5]isoxazole)oxy) propyloxy phenoxy acetate

A solution of methyl p-hydroxyphenoxy acetate (0.530 grams; 2.909 mmol) in dry methyl ethyl ketone (6 mL) was treated with 3-ethyl-6-(3-bromopropyl)oxy-7-propylbenz[4,5]isoxazole (0.790 grams; 2.424 mmol) and potassium carbonate (0.422 grams; 3.055 mmol). The mixture was refluxed for 12 hours. The reaction mixture was cooled to ambient and partitioned between isopropyl acetate and pH 4 buffer. The organic was washed with water, then dried over magnesium sulfate, filtered and evaporated *in vacuo* to an oil. Silica gel chromatography afforded the title compound.

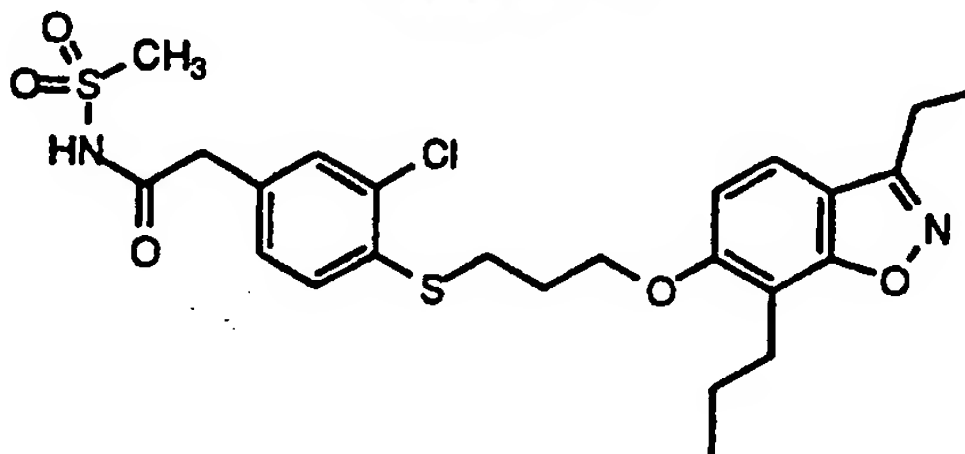
NMR (CDCl_3): 7.38 (d, 1H, $J = 8.6$ Hz); 6.90 (d, 1H, $J = 8.5$ Hz); 6.83 (apparent s, 4H); 4.57 (s, 2H); 4.21 (t, 2H, $J = 5.9$ Hz); 4.12 (t, 2H, $J = 5.8$ Hz); 3.78 (s, 3H); 2.94 (quart, 2H, $J = 7.4$ Hz); 2.84 (bt, 2H, $J = 7.9$ Hz).

3. 4-(3-(3-ethyl-7-propyl-6-benz[4,5]isoxazole)oxy)propyloxy phenoxy acetic acid

A solution of methyl 4-(3-(3-ethyl-7-propyl-6-benz[4,5]isoxazole) oxy)propyloxy phenoxy acetate (0.358 grams; 0.837 mmol) in methanol (4 mL) was treated with a solution of LiOH in water (1.299 M; 0.770 mL; 1.00 mmol). The solution was refluxed for 2 hours. The reaction was partitioned between isopropyl acetate and 0.1 N HCl. The organic was dried over magnesium sulfate, filtered and evaporated to an oil which was digested in cyclohexane/methylene chloride (1:1; 3 mL). Removal of volatiles under high vacuum afforded the title compound as a glass.

- 89 -

NMR (acetone): 7.68 (d, 1H, J = 8.6 Hz); 7.12 (d, 1H, J = 8.7 Hz); 6.88 (AB dd, 4H); 4.62 (s, 2H); 4.32 (t, 2H, J = 5.6 Hz); 4.20 (t, 2H, J = 5.6 Hz); 2.94 (quart, 2H, J = 7.5 Hz); 2.85 (bt, 2H, J = 7.5 Hz).

Example 28

N-Methylsulfonyl 3-chloro-4-(3-(3-ethyl-7-propyl-6-benz[4,5]isoxazole)oxy)propylthio phenyl acetamide

1. 3-chloro-4-(3-(3-ethyl-7-propyl-6-benz[4,5]isoxazole)oxy)propylthio phenyl acetamide

A solution of 3-chloro-4-(3-(3-ethyl-7-propyl-6-benz[4,5]isoxazole)oxy)propylthio phenyl acetic acid (L-165,461) (0.204 grams; 0.455 mmol) in dry methylene chloride (3 mL) was treated with dry DMF (5 μ L). Oxalyl chloride (0.048 mL; 0.546 mmol) was added dropwise and the solution stirred for 14 hours. All volatiles were removed *in vacuo* and the derived residue dissolved in dry THF (10 mL). Concentrated ammonia (1 mL) was added dropwise and the mixture stirred for 3 hours. The reaction was partitioned between isopropyl acetate and water. The organic was washed once more with water, then dried over magnesium sulfate. Filtration and evaporation afforded the title compound as a solid.

NMR (CDCl₃): 7.59 (d, 1H, J = 8.7 Hz); 7.40 (two overlapping d, 2H, J = 8.0, 1.9 Hz); 7.15 (dd, 1H, J = 8.1, 1.8 Hz); 7.09 (d, 1H, J = 8.8 Hz); 6.91 (vbs, 1H); 6.29 (vbs, 1H); 4.20 (t, 2H, J = 5.9 Hz); 3.48 (s, 2H); 3.27 (t, 2H, J = 7.2 Hz); 2.95 (quart, 2H, J = 7.4 Hz);

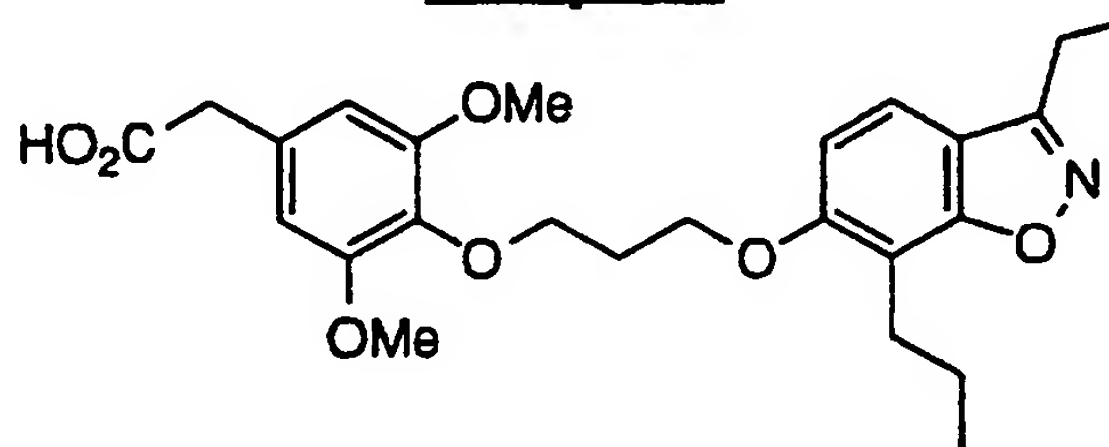
- 90 -

2. N-Methylsulfonyl 3-chloro-4-(3-(3-ethyl-7-propyl-6-benz[4,5]isoxazole)oxy)propylthio phenyl acetamide

A solution of 3-chloro-4-(3-(3-ethyl-7-propyl-6-benz[4,5]isoxazole)oxy)propylthio phenyl acetamide (L-783,573) (0.069 grams; 0.154 mmol) in dry toluene (2 mL) was treated with methanesulfonyl chloride (0.013 mL; 0.162 mmol) and 80% sodium hydride (0.005 grams; 0.162 mmol). The mixture was stirred at 80° C for 14 hours. The reaction mixture was partitioned between isopropyl acetate and 0.1 N HCl. The organic was dried over magnesium sulfate, filtered and concentrated to an oil which was chromatographed over silica gel to afford the title compound.

NMR (CDCl₃): 7.59 (d, 1H, J = 8.6 Hz); 7.43 (d, 1H, J = 8.1 Hz); 7.41 (d, 1H, J = 1.9 Hz); 7.27 (dd, 1H, J = 8.0, 2.0 Hz); 7.09 (d, 1H, J = 8.5 Hz); 4.30 (t, 2H, J = 5.8 Hz); 3.72 (s, 2H); 3.27 (t, 2H, J = 7.0 Hz); 3.22 (s, 3H); 2.94 (quart, 2H, J = 7.2 Hz); 2.88 (bt, 2H, J = 7.6 Hz).

Example 29



3,5-dimethoxy-4-(3-(3-(Ethyl)-7-(propyl)-6-benz-[4,5]-isoxazoloxy)propyloxy)phenyl acetic acid

Step A: Preparation of Methyl-3,5-dimethoxy-4-hydroxyphenyl acetate

A solution of 3,5-dimethoxy-4-hydroxyphenyl acetic acid (424mg) in methanol (2mL) was treated with excess trimethylsilyldiazomethane (2M in hexanes) at room temperature for 30min. The reaction was then treated with solid magnesium sulfate filtered and concentrated to yield the title compound (450mg). NMR

- 91 -

(CDCl₃); δ 8.20 (s,1H), 6.49 (s,2H), 3.72 (s,6H), 3.59 (s,3H), 3.52 (s,2H).

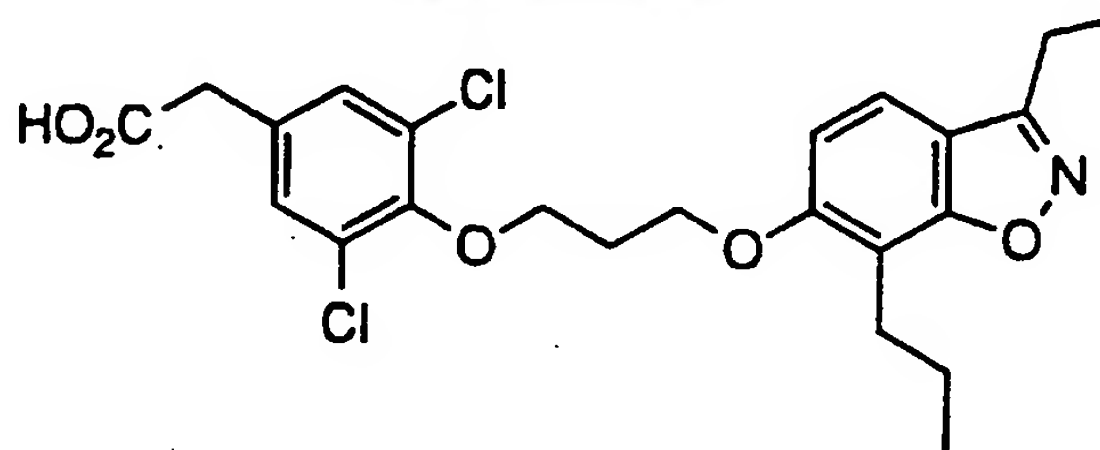
Step B: Preparation of Methyl-3,5-dimethoxy-4-(3-(3-(Ethyl)-7-(propyl)-6-benz-[4,5]-isoxazoloxy)propyloxy)phenyl acetate

The procedure from Example 76 Step C was followed using methyl-3,5-dimethoxy-4-hydroxyphenyl acetate (108mg) and 3-bromo-1-(3-(Ethyl)-7-(propyl)-6-benz-[4,5]-isoxazoloxy)propane (156mg) to afford a colorless oil (88mg). NMR (CDCl₃); δ 7.41 (d,2H), 6.99 (d,2H), 6.45 (s,2H), 3.76 (s,6H), 3.71 (s,3H), 3.55 (s,3H), 1.43 (t,3H), 0.92 (t,3H).

Step C: Preparation of 3,5-dimethoxy-4-(3-(3-(Ethyl)-7-(propyl)-6-benz-[4,5]-isoxazoloxy)propyloxy)phenyl acetic acid

Methyl-3,5-dimethoxy-4-(3-(3-(Ethyl)-7-(propyl)-6-benz-[4,5]-isoxazoloxy)propyloxy)phenyl acetate (80mg) was hydrolyzed according to the procedure found in Example 30 Step B to give the desired compound (68mg) as a colorless solid. NMR (CDCl₃); δ 7.41 (d,2H), 6.98 (d,2H), 6.45 (s,2H), 3.76 (s,6H), 3.58 (s,3H), 1.43 (t,3H), 0.92 (t,3H).

Example 30



3,5-dichloro-4-(3-(3-(Ethyl)-7-(propyl)-6-benz-[4,5]-isoxazoloxy)propyloxy)phenyl acetic acid

- 92 -

Step A: Preparation of Methyl 3,5-dichloro-4-hydroxy benzoate

A solution of 2,4-dichloro-4-hydroxybenzoic acid (414 mg) in ether (2mL) was treated with excess trimethylsilyl diazomethane (2M in hexanes). After 1 hour at room temperature the reaction was concentrated to yield an amber oil. The oil was chromatographed on silica gel to yield the title compound (220mg). NMR (CDCl₃); δ 7.80 (s,2H), 3.85 (s,3H).

Step B: Preparation of Methyl-3,5-dichloro-4-(3-(3-(Ethyl)-7-(propyl)-6-benz-[4,5]-isoxazoloxy)propyloxy)benzoate

The title compound was prepared according to Example 76 Step C using methyl 2,4-dichloro-4-hydroxy benzoate (112mg) and 3-bromo-1-(3-(Ethyl)-7-(propyl)-6-benz-[4,5]-isoxazoloxy)propane (165mg) to afford a slightly pink colored solid (220mg). NMR (CDCl₃); 8.0 (s,2H), 7.42 (d,2H), 6.96 (d,2H), 3.91 (s,3H), 1.42 (t,3H), 0.94 (t,3H).

Step C: Preparation of 3,5-dichloro-4-(3-(3-(Ethyl)-7-(propyl)-6-benz-[4,5]-isoxazoloxy)propyloxy)-benzoic acid

Methyl-2,5-dichloro-4-(3-(3-(Ethyl)-7-(propyl)-6-benz-[4,5]-isoxazoloxy)propyloxy)-benzoate (281mg) was hydrolyzed to give the title compound following the procedure of example 32 Step D as a colorless solid (227mg). NMR (CDCl₃); δ 7.90 (s,2H), 7.42 (d,2H), 6.95 (d,2H), 3.90 (s,3H), 1.41 (t,3H), 0.94 (t,3H).

Step D: Preparation of Methyl-3,5-dichloro-4-(3-(3-(Ethyl)-7-(propyl)-6-benz-[4,5]-isoxazoloxy)propyloxy)phenyl acetate

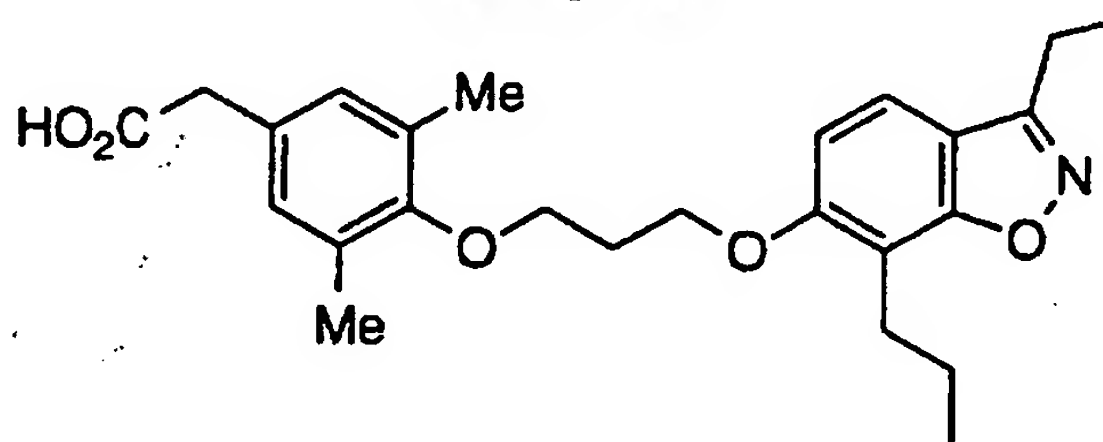
The title compound was prepared from 2,5-dichloro-4-(3-(3-(Ethyl)-7-(propyl)-6-benz-[4,5]-isoxazoloxy)propyloxy)-benzoic acid (202mg) following the procedure from Example 77, Step C, to give a colorless solid (177mg). NMR (CDCl₃); δ 7.42 (d,2H), 7.21 (s,2H), 6.96 (d,2H), 3.76 (s,3H), 3.54 (s,2H), 1.42 (t,3H), 0.97 (t,3H).

- 93 -

Step E: Preparation of 3,5-dichloro-4-(3-(3-(Ethyl)-7-(propyl)-6-benz-[4,5]-isoxazoloxy)propyloxy)phenyl acetic acid

Methyl-2,5-dichloro-4-(3-(3-(Ethyl)-7-(propyl)-6-benz-[4,5]-isoxazoloxy)propyloxy)phenyl acetate (37mg) was hydrolyzed according to the procedure found in Example 30 Step B to give a colorless solid (30mg). NMR (CDCl₃); δ 7.41 (d,2H), 7.20 (s,2H), 6.95 (d,2H), 3.59 (s,2H), 1.42 (t,3H), 0.95 (t, 3H).

Example 31



3,5-dimethyl-4-(3-(3-(Ethyl)-7-(propyl)-6-benz-[4,5]-isoxazoloxy)propyloxy)phenyl acetic acid

Step A: Preparation of Methyl-3,5-dimethylbenzoate

A solution of 3,5-dimethyl-4-hydroxybenzoic acid (1.0g) in ether (5mL) and methanol(5mL) was treated with excess trimethylsilyldiazomethane. After stirring 30min at room temperature the reaction was treated with magnesium sulfate, filtered and concentrated to a brown solid. The title compound was obtained by purification on silica gel to give a colorless solid (670mg). NMR (CDCl₃); δ 7.75 (s,2H), 3.85 (s,3H), 2.30 (s,6H).

Step B: Preparation of Methyl-3,5-dimethyl-4-(3-(3-(Ethyl)-7-(propyl)-6-benz-[4,5]-isoxazoloxy)propyloxy)benzoate

The title compound was prepared following the procedure for example 17, Step D, using methyl-3,5-dimethylbenzoate (500mg) and 3-bromo-1-(3-(Ethyl)-7-(propyl)-6-benz-[4,5]-isoxazoloxy)propane (890mg) as starting materials to give after silicagel chromatography

- 94 -

1.1g of a waxy solid. NMR (CDCl₃); δ 7.80 (s,2H), 7.42 (d,2H), 6.95 (d,2H), 3.85 (s,3H), 2.26 (s,3H), 1.40 (t,3H), 0.96 (t,3H).

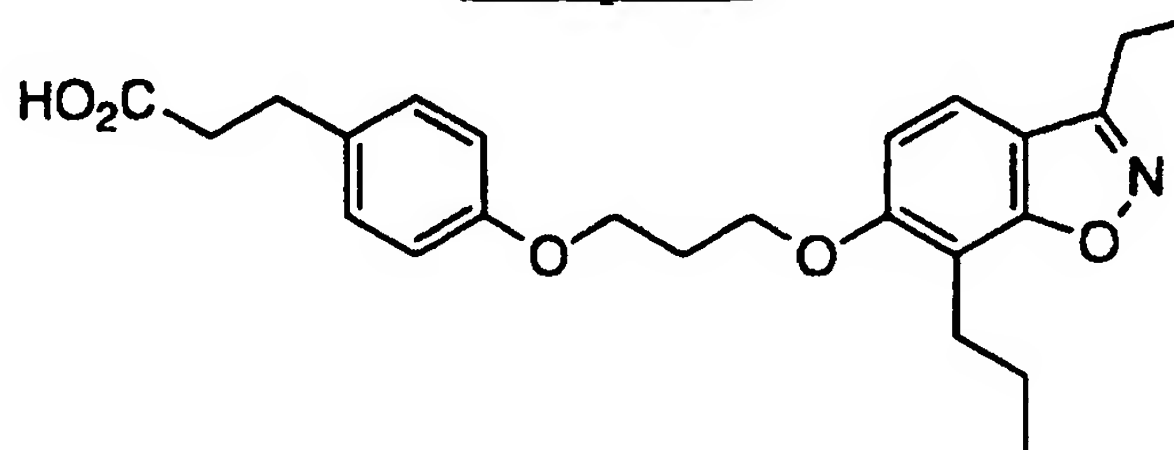
Step C: Preparation of Methyl-3,5-dimethyl-4-(3-(3-(Ethyl)-7-(propyl)-6-benz-[4,5]-isoxazoloxy)propyloxy)phenyl acetate

Methyl-3,5-dimethyl-4-(3-(3-(Ethyl)-7-(propyl)-6-benz-[4,5]-isoxazoloxy)propyloxy)benzoate (200mg) was hydrolyzed according to the procedure found in Example 77, Step C to give a waxy colorless solid (180mg). This material was then treated according to Example 77, Step C to give a colorless oil (88mg). NMR (CDCl₃); δ 7.41 (d,2H), 7.20 (s,2H), 6.94 (d,2H), 3.80 (s,3H), 3.52 (s,3H), 1.41 (t,3H), 0.95 (t,3H).

Step D: Preparation of 3,5-dimethyl-4-(3-(3-(Ethyl)-7-(propyl)-6-benz-[4,5]-isoxazoloxy)propyloxy)phenyl acetic acid

3,5-dimethyl-4-(3-(3-(Ethyl)-7-(propyl)-6-benz-[4,5]-isoxazoloxy)propyloxy)phenyl acetate (77mg) was hydrolyzed according to Example 30 Step B to give the desired compound (53mg). NMR (CDCl₃); δ 7.41 (d,2H), 7.22 (s,2H), 6.94 (d,2H), 3.51 (s,3H), 1.42 (t,3H), 0.96 (t,3H).

Example 32



4-(3-(3-(Ethyl)-7-(propyl)-6-benz-[4,5]-isoxazoloxy)-propyloxy)-phenyl propionic acid

Step A: Preparation of 3-(4-hydroxyphenyl)propionate:

- 95 -

In a 0°C ice bath, 3-(4-hydroxyphenyl)propionic acid (313.3 mg; 1.9 mmol), was dissolved in 3 ml of ether. Added to this solution was about 6 mL of diazomethane dissolved in ether (0.32 mmol/ mL). Allowed to stir for 5 minutes, vented the excess diazomethane with nitrogen to a colorless solution and concentrated *in vacuo* to afford a light yellow oil. Isolated 340.0 mg of the title compound and used without further purification. NMR: δ 7.07 (d,2H); 6.76 (d,2H); 3.68 (s,3H); 2.89 (t,2H); 2.62 (t,2H);

Step B: Preparation of 3-ethyl-6-hydroxy-7-propylbenz-[4,5]-isoxazole

The title compound was prepared by following the procedures from Example 7 Step A substituting commercially available 2,4-dihydroxy-3-propylpropiophenone, as a colorless solid. NMR 7.42 (d,2H), 6.98 (d,2H), 2.95 (q,2H), 2.84 (t,2H), 1.76 (m,2H), 1.42 (t,3H), 1.0 (t,3H).

Step C: Preparation of 3-ethyl-6-(3-bromopropyl)oxy-7-propylbenz-[4,5]-isoxazole

Following the procedure of Example 7 Step B and substituting 3-ethyl-6-hydroxy-7-propylbenz-[4,5]-isoxazole, the title compound was prepared as a colorless solid. NMR: δ 7.40 (d,1H); 6.92 (d,1H); 4.22 (t,2H); 3.69 (t,2H); 2.99 (q,2H); 2.84 (t,2H); 2.38 (m,2H); 1.41 (t,3H); 0.95 (t,3H)

Step D: Preparation of Methyl 4-(3-(3-(Ethyl)-7-(propyl)-6-benz-[4,5]-isoxazoloxy)propyloxy)-phenyl propionate

A mixture of 3-(4-hydroxyphenyl)propionate (73.7 mg; 0.409 mmol), (3-(3-(Ethyl)-7-(propyl)-6-benz-[4,5]-isoxazoloxy) bromide (146.7 mg; 0.45 mmol), cesium carbonate (139.7 mg; 0.43 mmol) and about 2.0 ml dry dimethylformamide was stirred and heated for 16 hours. It was concentrated *in vacuo*, diluted with water and extracted with ethyl acetate. The organic layer was washed with water, dried (Na₂SO₄), concentrated and chromatographed (silica gel, 30%

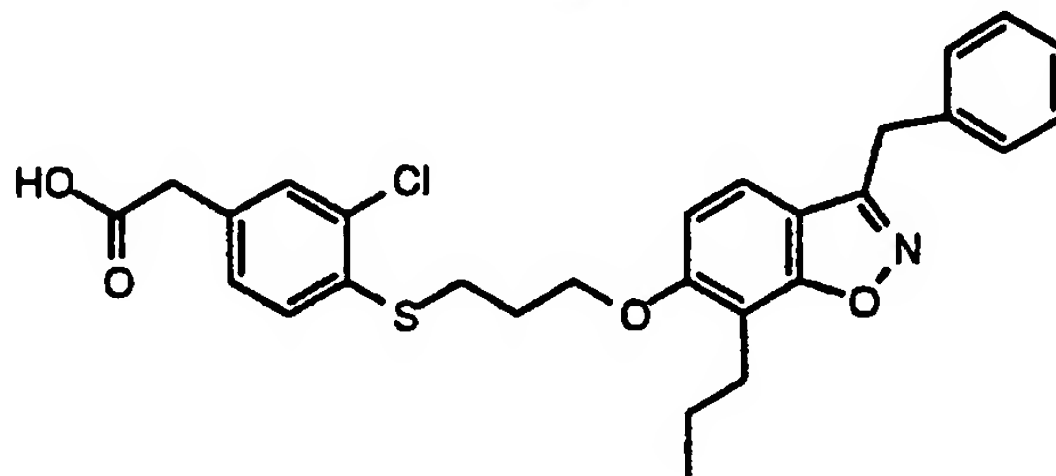
- 96 -

ethyl acetate in hexane) to yield 118.7 mg of the title compound as a light yellow oil. NMR: δ 7.20 (d,1H); 7.12 (d,2H); 6.92 (d,1H); 6.83 (d,2H); 4.28 (t,2H); 3.99 (t,2H); 3.69 (s,3H); 2.98 (q,2H); 2.90 (m,4H); 2.61 (m,2H); 2.32 (m,2H); 1.70 (m,2H); 1.43 (t,3H); 0.93 (t,3H)

Step E: Preparation of 4-(3-(3-(Ethyl)-7-(propyl)-6-benz-[4,5]-isoxazoloxy)-propyloxy)-phenyl propionic acid

A solution of 4-(3-(3-(Ethyl)-7-(propyl)-6-benz-[4,5]-isoxazoloxy)propyloxy)-phenyl (32.3 mg; 0.071 mmol), 1M LiOH (aq) (124 μ L) and methanol (2.0 mL) was heated at 60°C for 16 hours. The mixture was diluted with ethyl acetate and acidified to pH 5-6 with 1 M HCl, washed with water (2 times), brine (1 time) and dried over sodium sulfate and concentrated to afford 29.4 mg of the title compound. . MS 412 (M+H), NMR: δ 7.41 (d,1H); 7.13 (d,2H); 6.94 (d,1H); 6.87 (d,2H); 4.28 (t,2H); 4.20 (t,2H); 2.93 (m,6H); 2.66 (m,2H); 2.33 (m,2H); 1.68 (m,2H); 1.44 (t,3H); 0.95 (t,3H)

EXAMPLE 33



3-chloro-4-(3-phenylmethyl-7-(n-propyl)-6-benz[4,5]isoxazoloxy)propyl-thio)phenylacetic acid

Step A Preparation of 1,3-dihydroxy-4-phenylacetyl-2-(n-propyl)-benzene

Using the procedure in Example 51, step 1, phenylacetic acid and 2-(n-propyl)resorcinol were condensed in triflic acid to form 1,3-dihydroxy-4-phenylacetyl-2-(n-propyl)benzene.

- 97 -

NMR (CDCl₃): d 7.64 (d, 1H); 7.24 - 7.38 (m, 5H); 6.35 (d, 1H); 5.36 (s, 1H); 4.23 (s, 2H); 2.61 (t, 2H); 1.56 (m, 2H); 0.98 (t, 3H).

Step B Preparation of 6-hydroxy-3-phenylmethyl-7-(n-propyl)-benz[4,5]isoxazole

Using the procedures in Example 51, steps 2 and 3, 1,3-dihydroxy-4-phenylacetyl-2-(n-propyl)benzene was converted into 6-hydroxy-3-phenylmethyl-7-(n-propyl)benz[4,5]isoxazole.

NMR (CDCl₃): d 7.21 - 7.37 (m, 5H); 7.03 (d, 1H); 6.68 (d, 1H); 5.2 (bs, 1H); 4.26 (s, 2H); 2.85 (t, 2H); 1.72 (m, 2H); 1.00 (t, 3H).

Step C Preparation of methyl 3-chloro-4-(3-phenylmethyl-7-(n-propyl)-6-benz[4,5]isoxazoloxy)propylthio)phenylacetate

Using the procedure in Example 16, step 4, 6-hydroxy-3-phenylmethyl-7-(n-propyl)benz[4,5]isoxazole and methyl 3-chloro-4-(3-bromopropylthio)phenylacetate were heated in DMF with Cs₂CO₃ to prepare methyl 3-chloro-4-(3-phenylmethyl-7-(n-propyl)-6-benz[4,5]-isoxazoloxy)propylthio)phenylacetate

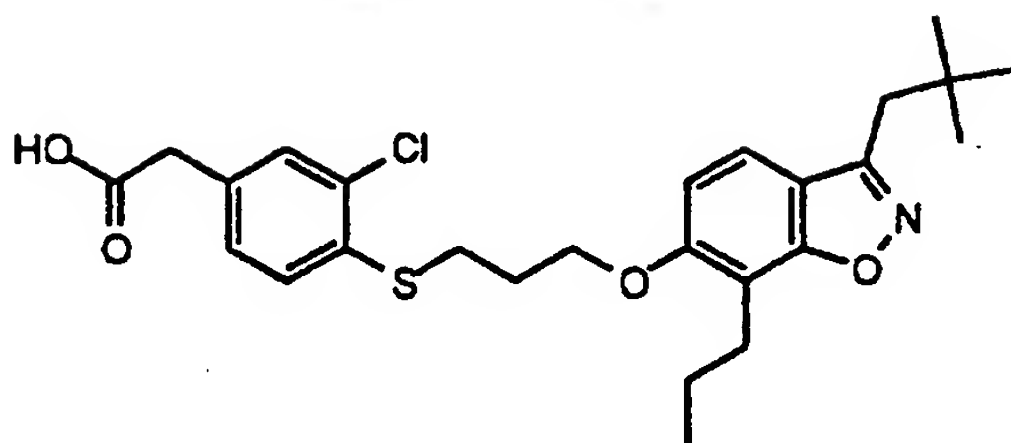
NMR (CDCl₃): d 7.22 - 7.35 (m, 5H); 7.12 (m, 2H); 6.79 (d, 1H); 4.29 (s, 2H); 4.13 (t, 2H); 3.71 (s, 3H); 3.55 (s, 2H); 3.15 (t, 2H); 2.86 (t, 2H); 2.16 (m, 2H); 1.69 (m, 2H); 0.95 (t, 3H).

Step D Preparation of 3-chloro-4-(3-phenylmethyl-7-(n-propyl)-6-benz[4,5]isoxazoloxy)propylthio)phenylacetic acid

Using the procedure in Example 2, methyl 3-chloro-4-(3-phenylmethyl-7-(n-propyl)-6-benz[4,5]isoxazoloxy)propylthio)phenyl acetate was saponified with LiOH to form 3-chloro-4-(3-phenylmethyl-7-(n-propyl)-6-benz[4,5]isoxazoloxy)propylthio)phenylacetic acid

NMR (DMSO-d₆): d 7.43 (d, 1H); 7.20 - 7.39 (m, 4H); 7.13 (dd, 1H); 7.04 (d, 1H); 4.30 (s, 2H); 4.16 (t, 2H); 3.30 (s, 2H); 3.12 (t, 2H); 2.77 (t, 2H); 2.04 (m, 2H); 1.59 (m, 2H); 0.87 (t, 3H).

- 98 -

EXAMPLE 34

3-chloro-4-(3-(2,2-dimethylpropyl)-7-(n-propyl)-6-benz[4,5]isoxazoloxy)-propylthio)phenylacetic acid

Step A Preparation of 1,3-dihydroxy-4-(3,3-dimethylbutyryl)-2-(n-propyl)benzene

Using the procedure in Example 51, step 1, 3,3-dimethylbutyric acid and 2-(n-propyl)resorcinol were condensed in triflic acid to form 1,3-dihydroxy-4-(3,3-dimethylbutyryl)-2-(n-propyl)benzene
NMR (CDCl₃): d 7.53 (d, 1H); 6.32 (d, 1H); 2.86 (s, 2H); 2.62 (t, 2H); 1.59 (m, 2H); 1.06 (s, 9H); 0.98 (t, 3H).

Step B Preparation of 3-(2,2-dimethylpropyl)-6-hydroxy-7-(n-propyl)benz[4,5]isoxazole

Using the procedures in Example 51, steps 2 and 3, 1,3-dihydroxy-4-(3,3-dimethylbutyryl)-2-(n-propyl)benzene was converted into 3-(2,2-dimethylpropyl)-6-hydroxy-7-(n-propyl)benz[4,5]isoxazole
NMR (CDCl₃): d 7.29 (d, 1H); 6.80 (d, 1H); 5.30 (vbs, 1H); 2.87 (t, 2H); 2.80 (s, 2H); 1.75 (m, 2H); 1.04 (s, 9H); 1.00 (t, 3H).

Step C Preparation of methyl 3-chloro-4-(3-(2,2-dimethylpropyl)-7-(n-propyl)-6-benz[4,5]isoxazoloxy)propylthio)-phenylacetate

Using the procedure in Example 16, step 4, 3-(2,2-dimethylpropyl)-6-hydroxy-7-(n-propyl)benz[4,5]isoxazole and methyl 3-chloro-4-(3-bromopropylthio)phenylacetate were heated in DMF with Cs₂CO₃ to prepare methyl 3-chloro-4-(3-(2,2-dimethylpropyl)-7-(n-propyl)-6-benz[4,5]isoxazoloxy)propylthio)phenylacetate

- 99 -

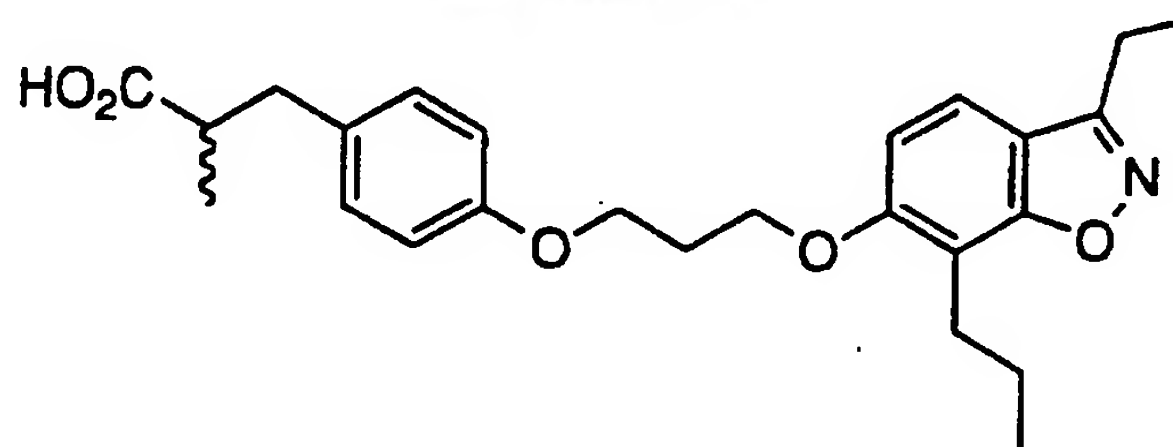
NMR (CDCl₃): d 7.37 (d, 1H); 7.25 - 7.33 (m, 2H); 7.12 (dd, 1H); 6.90 (d, 1H); 4.19 (t, 2H); 3.70 (s, 3H); 3.55 (s, 2H); 3.18 (t, 2H); 2.89 (t, 2H); 2.81 (s, 2H); 2.20 (m, 2H); 1.71 (m, 2H); 1.05 (s, 9H); 0.96 (t, 3H).

Step D Preparation of 3-chloro-4-(3-(2,2-dimethylpropyl)-7-(n-propyl)-6-benz[4,5]isoxazoloxy)propylthio)phenylacetic acid

Using the procedure in Example 2, methyl 3-chloro-4-(3-(2,2-dimethylpropyl)-7-(n-propyl)-6-benz[4,5]isoxazoloxy)propylthio)phenyl acetate was saponified with LiOH to form 3-chloro-4-(3-(2,2-dimethylpropyl)-7-(n-propyl)-6-benz[4,5]isoxazoloxy)propylthio)phenylacetic acid

NMR (CDCl₃): d 7.36 (d, 1H); 7.26 - 7.35 (m, 2H); 7.13 (dd, 1H), 6.89 (d, 1H); 4.19 (t, 2H); 3.60 (s, 2H); 3.17 (t, 2H); 2.86 (t, 2H); 2.81 (s, 2H); 2.19 (m, 2H); 1.70 (m, 2H); 1.04 (s, 9H); 0.95 (t, 3H).

Example 35



2-methyl-4-(3-(3-(Ethyl)-7-(propyl)-6-benz-[4,5]-isoxazoloxy)propyloxy)-phenyl propionic acid

Step A: Preparation of Preparation of Methyl-2-methyl-4-(3-(3-(Ethyl)-7-(propyl)-6-benz-[4,5]-isoxazoloxy)propyloxy)-phenyl propionate

A solution of Methyl 4-(3-(3-(Ethyl)-7-(propyl)-6-benz-[4,5]-isoxazoloxy)propyloxy)-phenyl propionate from Example 32 Step C (16.5mg, 0.36 mmol) in THF (0.5mL) at -78°C, under nitrogen was treated with KHMDS (0.08mL, 0.5 M in toluene) and stirred for 30min. Excess methyl iodide was then added and the reaction stirred 30 min

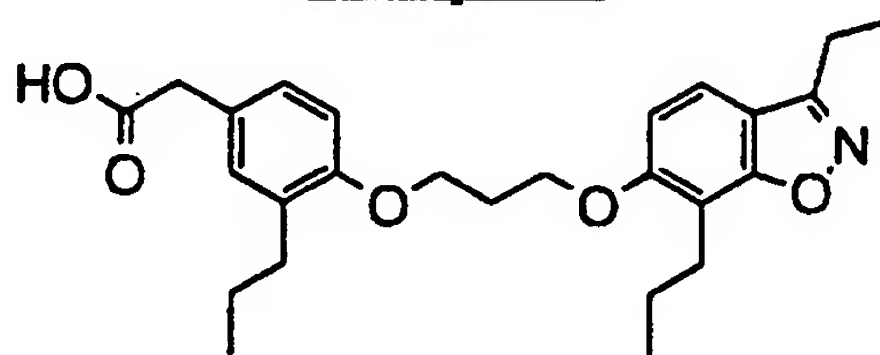
- 100 -

longer then warmed to RT. After 45 min the reaction was treated with 1M ammonium chloride and extracted with ethyl acetate (x2), dried over anhydrous sodium sulfate, filtered and concentrated. The title compound was obtained after purification by silica gel chromatography to give a colorless oil (12mg, 76%) NMR (CDCl₃); δ 7.41 (d,2H), 7.09 (d, 2H), 6.95 (d, 2H), 6.83 (d,2H), 3.65 (s,3H), 1.43 (t,3H), 1.16 (d,2H), 0.90 (t,3H).

Step B: Preparation of 2-methyl-4-(3-(3-(Ethyl)-7-(propyl)-6-benz-[4,5]-isoxazoloxy)propyloxy)-phenyl propionic acid

A solution of methyl-2-methyl-4-(3-(3-(Ethyl)-7-(propyl)-6-benz-[4,5]-isoxazoloxy)propyloxy)-phenyl propionate (11.5 mg, Step A) was dissolved in MeOH (0.5mL) and 1M LiOH (0.10mL) was added. The resulting solution was warmed to 50°C for 2 hours, cooled and concentrated. The residue was partitioned between ethyl acetate and 1M Hcl. The organic fraction was removed, dried and concentrated to give the title compound as a colorless oil (10.7 mg) NMR (CDCl₃); δ 7.40 (d,2H), 7.11 (d,2H), 6.95 (d,2H), 6.85 (d,2H), 1.43 (t,3H), 1.18 (d,2H), 0.95 (t,3H).

Example 36



3-Propyl-4-(3-(3-ethyl-7-propyl-6-benz-[4,5]-isoxazoloxy)-propyloxy)phenylacetic acid

Step A: Preparation of methyl 3-propyl-4-(3-(3-ethyl-7-propyl-6-benz-[4,5]-isoxazoloxy)-propyloxy)phenylacetate

Using the method of Example 17, Step D, 1-bromo-3-(3-ethyl-7-propyl-6-benz-[4,5]-isoxazoloxy)phenoxypropane as the starting material, the title compound was obtained.

- 101 -

^1H NMR(400MHz, CDCl_3): δ 7.37 (d, 1H, $J = 8.6$ Hz), 7.01 (m, 2H), 6.90 (d, 1H, $J = 8.5$ Hz), 6.78 (d, 1H, $J = 8.3$ Hz), 4.24 (t, 2H, $J = 6.1$ Hz), 4.15 (t, 2H, $J = 6.0$ Hz), 3.65 (s, 3H), 3.52 (s, 2H), 2.94 (quart, 2H, $J = 7.6$ Hz), 2.82 (t, 2H, $J = 7.7$ Hz), 2.53 (t, 2H, $J = 7.7$ Hz), 2.29 (quint, 2H, $J = 6.0$ Hz), 1.66 (hex, 2H, $J = 7.5$ Hz), 1.57 (hex, 2H, $J = 7.6$ Hz), 1.41 (t, 3H, $J = 7.6$ Hz), 0.89 (m, 6H).

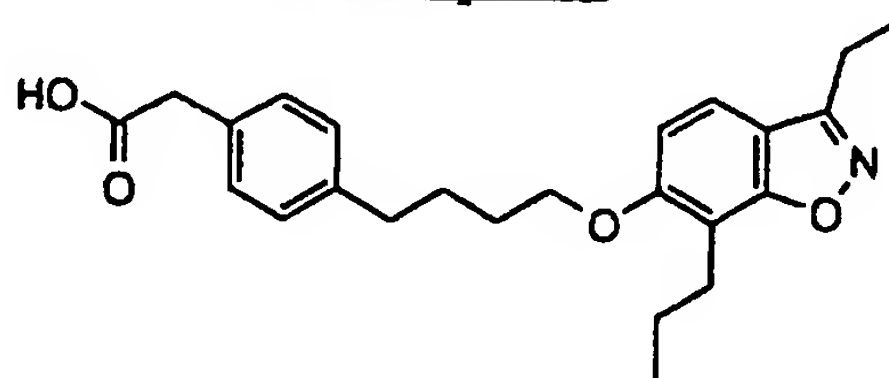
Step B: Preparation of 3-propyl-4-(3-(3-ethyl-7-propyl-6-benz-[4,5]-isoxazoloxy)-propyloxy)phenylacetic acid

Using the method of Example 18, methyl 3-propyl-4-(3-(3-ethyl-7-propyl-6-benz-[4,5]-isoxazoloxy)- propyloxy)phenylacetate as the starting material, the title compound was obtained.

^1H NMR(400MHz, CDCl_3): δ 7.37 (d, 1H, $J = 8.6$ Hz), 7.01 (m, 2H), 6.90 (d, 1H, $J = 8.5$ Hz), 6.78 (d, 1H, $J = 8.3$ Hz), 4.24 (t, 2H, $J = 6.1$ Hz), 4.15 (t, 2H, $J = 6.0$ Hz), 3.52 (s, 2H), 2.94 (quart, 2H, $J = 7.6$ Hz), 2.82 (t, 2H, $J = 7.7$ Hz), 2.53 (t, 2H, $J = 7.7$ Hz), 2.29 (quint, 2H, $J = 6.0$ Hz), 1.66 (hex, 2H, $J = 7.5$ Hz), 1.57 (hex, 2H, $J = 7.6$ Hz), 1.41 (t, 3H, $J = 7.6$ Hz), 0.89 (m, 6H).

ESI: MS $m/e = 440$ (M+1)

Example 37



4-(3-(3-(Ethyl)-7-propyl-6-benz-[4,5]-isoxazoloxy)butyl)phenylacetate

Step A: Preparation of methyl 4-(4-hydroxybutyn-1-yl)phenylacetate

To a solution of methyl 4-bromophenylacetate (229 mg, 1.0 mmole) and 3-butyn-1-ol (151 μL , 2.0 mmole) in triethylamine (4.0 mL) was added cuprous bromide (18 mg, 0.12 mmole) and tetra(triphenylphosphine)palladium (46 mg, 0.04 mmole), and the

- 102 -

mixture refluxed under a nitrogen atmosphere for 1 hr 20 min. The mixture was evaporated *in vacuo* and the residue partitioned with water and ether. The organic phase was washed with brine, dried over magnesium sulfate and concentrated *in vacuo* to an oil. Flash chromatography on silica gel in 7:3 hexane:ethyl acetate afforded the title compound (175 mg) as an oil. NMR (CDCl₃): δ 1.69 (s, 1H); 2.71 (t, 2H); 3.63 (s, 2H); 3.71 (s, 3H); 3.83 (t, 2H); 7.22 (d, 2H); 7.38 (d, 2H).

Step B: Preparation of methyl 4-(4-hydroxybutyl)phenylacetate

A solution of methyl 4-(4-hydroxybutyn-1-yl)phenylacetate (178 mg, 0.82 mmole) and 10% palladium on carbon (30 mg) in ethanol (2 mL) were stirred under a balloon of hydrogen for 3 days at room temperature. The mixture was filtered and the filtrate concentrated *in vacuo* to give the title compound (181 mg) as an oil. NMR (CDCl₃): δ 1.52 (s, 1H); 1.64 (m, 2H); 1.71 (m, 2H); 2.65 (t, 2H); 3.61 (s, 2H); 3.68 (t, 2H); 3.71 (s, 3H); 7.15 (d, 2H); 7.21 (d, 2H).

Step C: Preparation of methyl 4-(4-methansulfonyloxybutyl)-phenylacetate

To a solution of methyl 4-(4-hydroxybutyl)phenylacetate (170 mg, 0.77 mmole) in methylene chloride (2 mL) was added methansulfonyl anhydride (146 mg, 1.06 mmole), pyridine (187 μ L, 2.31 mmole) and 4-dimethylaminopyridine (5 mg, 0.04 mmole) and the mixture stirred at room temperature for 2 hours. The mixture was concentrated *in vacuo* and the residue dissolved in ethyl acetate and washed with 1N HCl, water, brine, dried over magnesium sulfate and concentrated *in vacuo* to give the title compound (187 mg) as an oil. NMR (CDCl₃): δ 1.77 (m, 4H); 2.66 (t, 2H); 3.00 (s, 3H); 3.62 (s, 2H); 3.71 (s, 3H); 4.25 (t, 2H); 7.15 (d, 2H); 7.22 (d, 2H).

Step D: Preparation of methyl 4-(3-(3-(ethyl)-7-propyl-6-benz-[4,5]-isoxazoloxy)butyl)phenylacetate

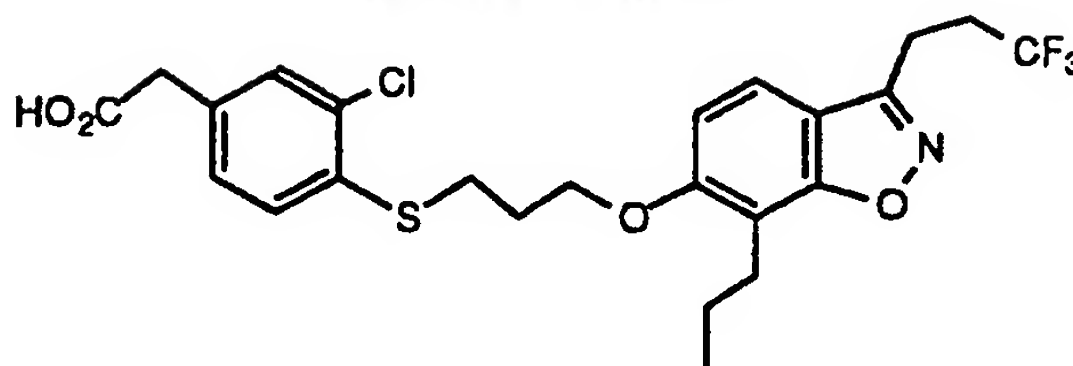
- 103 -

A suspension of sodium hydride (15 mg, 0.36 mmole) in DMF (1.5 mL) was treated with 3-ethyl-6-hydroxy-7-propylbenz-[4,5]-isoxazole (68 mg, 0.33 mmole) and the mixture stirred at room temperature for 10 minutes under a nitrogen atmosphere. A solution of methyl 4-(4-methansulfonyloxybutyl)phenylacetate (100 mg, 0.33 mmole) in DMF (0.5 mL) was added and the mixture stirred at 80°C for 5 hours. The cooled reaction mix was dissolved in ethyl acetate and washed with water (twice), brine, dried over magnesium sulfate and concentrated *in vacuo* to an oil. The crude product was purified by thin layer chromatography on silica gel eluting with hexane:ethyl acetate (4:1) to give the title compound (80 mg) as an oil. NMR (CDCl₃): δ 0.97 (t, 3H); 1.44 (t, 3H); 1.71 (m, 2H); 1.87 (m, 4H); 2.71 (t, 2H); 2.88 (t, 2H); 2.97 (q, 2H); 3.62 (s, 2H); 3.71 (s, 3H); 6.89 (d, 1H); 7.18 (d, 2H); 7.22 (d, 2H); 7.39 (d, 1H).

Step E: Preparation of 4-(3-(3-(ethyl)-7-propyl-6-benz-[4,5]-isoxazoloxy)butyl)phenylacetate

To a solution of methyl 4-(3-(3-(ethyl)-7-propyl-6-benz-[4,5]-isoxazoloxy)butyl)phenylacetate (80 mg, 0.195 mmole) in methanol (2 mL) was added a solution of lithium hydroxide (1M, 390 μ L), and the resulting solution stirred at 60°C for 2 hours. The solution was concentrated *in vacuo* and the residue partitioned with ethyl acetate and 1NHCl. The aqueous phase was washed with ethyl acetate and the combined organic extracts washed with water, brine, dried over magnesium sulfate and concentrated *in vacuo* to afford the title compound (76 mg) as an oil. NMR (CDCl₃): δ 0.968 (t, 3H); 1.44 (t, 3H); 1.71 (m, 2H); 1.87 (m, 4H); 2.71 (t, 2H); 2.88 (t, 2H); 2.97 (q, 2H); 3.65 (s, 2H); 4.07 (t, 2H); 6.89 (d, 1H); 7.19 (d, 2H); 7.23 (d, 2H); 7.39 (d, 1H). Mass spec, $m/e = 396 (m + 1)$.

- 104 -

EXAMPLE 38

3-chloro-4-(7-(n-propyl)-3-(3,3,3-trifluoropropyl)-6-benz[4,5]isoxazol-2-ylpropylthio)phenylacetic acid

Step A Preparation of 1,3-dihydroxy-2-(n-propyl)-4-(4,4,4-trifluoro-butyryl)benzene

Using the procedure in Example 51, step 1, 4,4,4-trifluoro-butyric acid and 2-(n-propyl)resorcinol were condensed in triflic acid to form 1,3-dihydroxy-2-(n-propyl)-4-(4,4,4-trifluorobutyryl)benzene

NMR (CDCl₃): d 7.52 (d, 1H); 6.38 (d, 1H); 5.42 (s, 1H); 3.22 (t, 2H); 2.62 (t, 2H); 2.59 (m, 2H); 1.58 (m, 2H); 0.98 (t, 3H).

Step B Preparation of 6-hydroxy-7-(n-propyl)-3-(3,3,3-trifluoropropyl)benz[4,5]isoxazole

Using the procedures in Example 51, steps 2 and 3, 1,3-dihydroxy-2-(n-propyl)-4-(4,4,4-trifluorobutyryl)benzene was converted into 6-hydroxy-7-(n-propyl)-3-(3,3,3-trifluoropropyl)benz[4,5]isoxazole

NMR (CDCl₃): d 7.31 (d, 1H); 6.84 (d, 1H); 5.31 (vbs, 1H); 3.18 (m, 2H); 2.86 (t, 2H); 2.70 (m, 2H); 1.74 (m, 2H); 0.99 (t, 3H).

Step C Preparation of methyl 3-chloro-4-(7-(n-propyl)-3-(3,3,3-trifluoropropyl)-6-benz[4,5]isoxazol-2-ylpropylthio)phenylacetate

Using the procedure in Example 16, step 4, 6-hydroxy-7-(n-propyl)-3-(3,3,3-trifluoropropyl)benz[4,5]isoxazole and methyl 3-chloro-4-(3-bromopropylthio)phenylacetate were heated in DMF with Cs₂CO₃ to prepare methyl 3-chloro-4-(7-(n-propyl)-3-(3,3,3-trifluoropropyl)-6-benz[4,5]isoxazol-2-ylpropylthio)phenylacetate

- 105 -

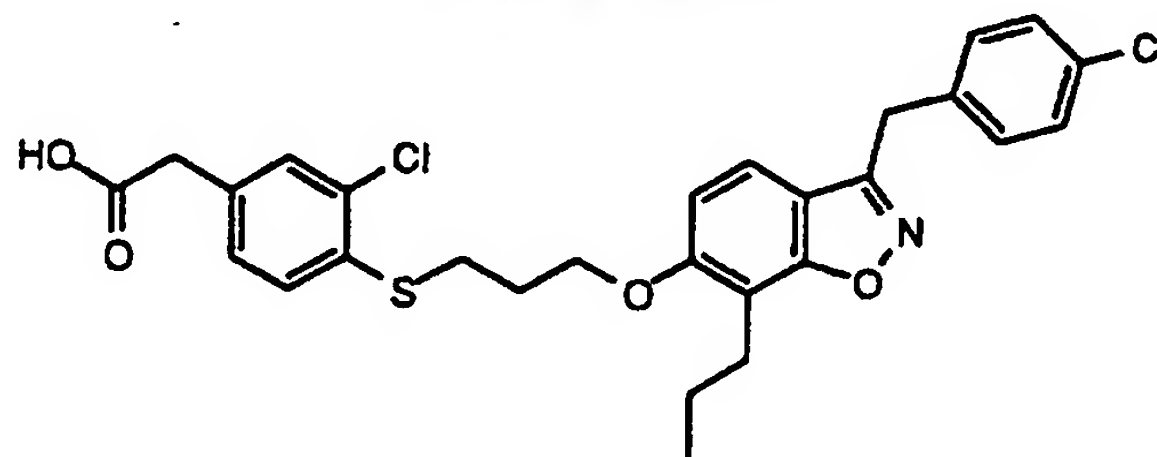
NMR (CDCl₃): d 7.38 (d, 1H); 7.25 - 7.33 (m, 2H); 7.13 (dd, 1H); 6.93 (d, 1H); 4.21 (t, 2H); 3.71 (s, 3H); 3.56 (s, 2H); 3.19 (m, 4 H); 2.89 (t, 2H); 2.72 (m, 2H); 2.21 (m, 2H); 1.70 (m, 2H); 0.95 (t, 3H).

Step D Preparation of 3-chloro-4-(7-(n-propyl)-3-(3,3,3-trifluoropropyl)-6-benz[4,5]isoxazoloxy)propylthio)phenylacetic acid

Using the procedure in Example 2, methyl 3-chloro-4-(7-(n-propyl)-3-(3,3,3-trifluoropropyl)-6-benz[4,5]isoxazoloxy)propylthio)-phenylacetate was saponified with LiOH to form 3-chloro-4-(7-(n-propyl)-3-(3,3,3-trifluoropropyl)-6-benz[4,5]isoxazoloxy)propylthio)phenylacetic acid.

NMR (CDCl₃): d 7.39 (d, 1H); 7.26 - 7.34 (m, 2H); 7.13 (dd, 1H); 6.92 (d, 1H); 4.20 (t, 1H); 3.60 (s, 2H); 3.19 (m, 2H); 2.87 (t, 2H); 2.71 (m, 2H); 2.20 (m, 2H); 1.69 (m, 2H); 0.95 (t, 3H).

EXAMPLE 39



3-chloro-4-(3-(4-chlorophenylmethyl)-7-(n-propyl)-6-benz[4,5]isoxazol-oxo)propylthio)phenylacetic acid

Step A Preparation of 4-(4-chlorophenylacetyl)-1,3-dihydroxy-2-(n-propyl)benzene

Using the procedure in Example 51, step 1, 4-chlorophenyl-acetic acid and 2-(n-propyl)resorcinol were condensed in triflic acid to form 4-(4-chlorophenylacetyl)-1,3-dihydroxy-2-(n-propyl)benzene.

NMR (CDCl₃): d 7.60 (d, 1H); 7.31 (d, 2H); 7.20 (d, 2H); 6.35 (d, 1H); 4.19 (s, 2H); 2.61 (t, 2H); 1.59 (m, 2H); 0.96 (t, 3H).

- 106 -

Step B Preparation of 3-(4-chlorophenylmethyl)-6-hydroxy-7-(n-propyl)benz[4,5]isoxazole

Using the procedure in Example 51, step 4-(4-chlorophenyl-acetyl)-1,3-dihydroxy-2-(n-propyl)benzene was converted into 3-(4-chlorophenylmethyl)-6-hydroxy-7-(n-propyl)benz[4,5]isoxazole

NMR (CDCl₃): d 7.27 (q, 4H); 7.03 (d, 1H); 6.71 (d, 1H); 5.14 (bs, 1H); 4.24 (s, 2H); 2.85 (t, 2H); 1.73 (m, 2H); 1.00 (t, 3H).

Step C Preparation of methyl 3-chloro-4-(3-(4-chlorophenylmethyl)-7-(n-propyl)-6-benz[4,5]isoxazoloxy)propylthio)phenylacetate

Using the procedure in Example 16, step 4, 6-hydroxy-3-(4-chlorophenylmethyl)-7-(n-propyl)benz[4,5]isoxazole and methyl 3-chloro-4-(3-bromopropylthio)phenylacetate were heated in DMF with Cs₂CO₃ to prepare methyl 3-chloro-4-(3-(4-chlorophenylmethyl)-7-(n-propyl)-6-benz[4,5]-isoxazoloxy)propylthio)phenyl acetate

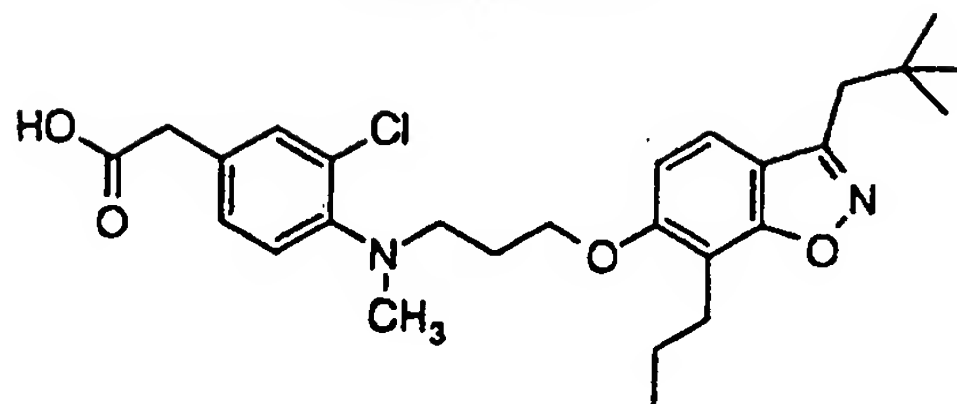
NMR (CDCl₃): d 7.23 - 7.32 (m, 6H); 7.12 (dd, 1H); 7.10 (d, 1H); 6.71 (d, 1H); 4.25 (s, 2H); 4.15 (t, 2H); 3.71 (s, 3H); 3.54 (s, 2H); 3.15 (t, 2H); 2.86 (t, 2H); 2.17 (m, 2H); 1.69 (m, 2H); 0.95 (t, 3 H).

Step D Preparation of 3-chloro-4-(3-(4-chlorophenylmethyl)-7-(n-propyl)-6-benz[4,5]isoxazoloxy)propylthio)phenylacetic acid

Using the procedure in Example 2, methyl 3-chloro-4-(3-(4-chlorophenylmethyl)-7-(n-propyl)-6-benz[4,5]isoxazoloxy)propylthio)-phenyl acetate was saponified with LiOH to form 3-chloro-4-(3-(4-chlorophenylmethyl)-7-(n-propyl)-6-benz[4,5]isoxazoloxy)propyl-thio)phenylacetic acid

NMR (DMSO-d₆): d 7.46 (d, 1H); 7.34 - 7.41 (q, 4H); 7.27 - 7.34 (m, 2H); 7.13 (dd, 1H); 7.04 (d, 1H); 4.31 (s, 2H); 4.17 (t, 2H); 3.29 (s, 2H); 3.14 (t, 2H); 2.78 (t, 2H); 2.04 (m, 2H); 1.59 (m, 2H); 0.86 (t, 3 H).

- 107 -

Example 40

3-Chloro-4-(3-(3-(2,2-dimethylpropyl)-7-propyl-6-benz-[4,5]-isoxazoloxy)propyl-N-methylamino)phenylacetate

Step A: Preparation of Methyl 3-Chloro-4-(3-(3-(2,2-dimethylpropyl)-7-propyl-6-benz-[4,5]-isoxazoloxy)propyl-N-methylamino)phenylacetate

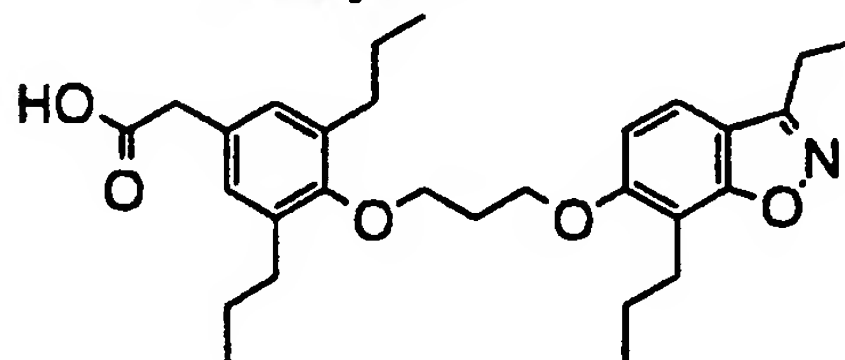
Sodium cyanoborohydride (10.5 mg, 0.16 mmole) was added in portions to a solution of methyl 3-chloro-4-(3-(3-(2,2-dimethylpropyl)-7-propyl-6-benz-[4,5]-isoxazoloxy)propylamino)phenylacetate (obtained as the product in Example 21, 50 mg, 0.102 mmole), 37% formaldehyde (92 μ L, 1.02 mmole) and bromocresol green solution (0.04%, 1 drop) in acetonitrile (1 mL) at room temperature. The mixture was stirred for 1 hour during which time acetic acid was added to maintain an acid pH (yellow indicator color). The mixture was diluted with ethyl acetate and washed with ice-cold 2.5M sodium hydroxide (2x), water (2x), brine, dried over magnesium hydroxide and concentrated *in vacuo* to give the title compound (51 mg) as gum. NMR (CD_3OD); δ 0.904 (t, 3H); 1.03 (s, 9H); 1.63 (m, 2H); 2.07 (m, 2H); 2.77 (s, 2H); 2.82 (t, 2H); 2.82 (s, 3H); 3.27 (t, 2H); 3.57 (s, 2H); 3.67 (s, 3H); 4.17 (t, 2H); 7.01 (d, 1H); 7.14 (m, 2H); 7.27 (s, 1H); 7.49 (d, 1H).

Step B: Preparation of 3-Chloro-4-(3-(3-(2,2-dimethylpropyl)-7-propyl-6-benz-[4,5]-isoxazoloxy)propyl-N-methylamino(phenylacetate)

Using the method of Example 22, substituting methyl 3-chloro-4-(3-(3-(2,2-dimethylpropyl)-7-propyl-6-benz-[4,5]-isoxazoloxy)propyl-N-methylamino)phenylacetate as starting material, the title compound was obtained. NMR (CD_3OD); δ 0.91 (t, 3H); 1.03

- 108 -

(s, 9H); 1.64 (m, 2H); 2.06 (m, 2H); 2.77 (s, 2H); 2.82 (t, 2H); 2.82 (s, 3H); 3.26 (t, 2H); 3.52 (s, 2H); 4.17 (t, 2H); 7.01 (d, 1H); 7.15 (s, 2H); 7.29 (s, 1H); 7.49 (d, 1H). Mass spec, $m/e = 488$ ($m + 1$).

Example 41

3,5-Dipropyl-4-(3-(3-ethyl-7-propyl-6-benz-[4,5]-isoxazoloxy)-propyloxy)phenylacetic acid

Step A: Preparation of methyl 3-allyl-4-allyloxyphenylacetate

A solution of methyl 3-allyl-4-hydroxyphenylacetate (4.10 g)(Example 17, Step B), allyl bromide (2.30 mL) and potassium carbonate (3.95 g) in 2-butanone (40 mL) was refluxed for four hours. The mixture was partitioned between 0.2N HCl and ethyl acetate. The organic layer was dried over magnesium sulfate, filtered, concentrated in vacuo. Column Chromatography (silica gel 60, 50% methylene chloride in hexane) gave the title compound.

^1H NMR(400MHz, CDCl_3): δ 7.04 (m, 2H), 6.76 (d, 1H, $J = 8.2$ Hz), 6.08-5.92 (m, 2H), 5.41-5.01 (m, 4H), 4.49 (m, 2H), 3.66 (s, 3H), 3.52 (s, 2H), 3.37 (d, 2H, $J = 6.7$ Hz).

Step B: Preparation of methyl 3,5-diallyl-4-hydroxyphenylacetate

Using the method of Example 17, Step B, methyl 3-allyl-4-allyloxyphenylacetate as the starting material, the title compound was obtained.

^1H NMR(400Mhz, CDCl_3): δ 6.90 (s, 2H), 5.98-5.94 (m, 2H), 5.14 (m, 5H), 3.66 (s, 3H), 3.49 (s, 2H), 3.37 (d, 4H, $J = 6.5$ Hz)

Step C: Preparation of methyl 3,5-dipropyl-4-hydroxyphenylacetate

- 109 -

Using the method of Example 17, Step C, methyl 3,5-diallyl-4-hydroxyphenylacetate as the starting material, the title compound was obtained.

¹H NMR(400MHz, CD₃COCD₃): δ 6.88 (s, 2H), 4.62 (s, 1H), 3.68 (s, 3H), 3.51 (s, 2H), 2.54 (t, 4H, J = 7.6 Hz), 1.62 (hex, 4H, J = 7.5 Hz), 0.98 (t, 6H, J = 7.4 Hz).

Step D: Preparation of methyl 3,5-dipropyl-4-(3-(3-ethyl-7-propyl-6-benz-[4,5]-isoxazoloxy)-propyloxy)phenylacetate

Using the method of Example 17, Step D, methyl 3,5-dipropyl-4-hydroxyphenylacetate and 1-bromo-3-(3-ethyl-7-propyl-6-benz-[4,5]-isoxazoloxy)phenoxypropane as the starting material, the title compound was obtained.

¹H NMR(400MHz, CDCl₃): δ 7.39 (d, 1H, J = 8.5 Hz), 6.94 (d, 1H, J = 8.6 Hz), 6.90 (m, 2H), 4.31 (t, 2H, J = 5.9 Hz), 3.94 (t, 2H, J = 5.9 Hz), 3.66 (s, 3H), 3.51 (s, 2H), 2.95 (quart, 2H, J = 7.5 Hz), 2.85 (t, 2H, J = 7.3 Hz), 2.52 (m, 4H), 2.28 (quint, J = 6.5 Hz), 1.71-1.52 (m, 6H), 1.40 (t, 3H, J = 7.3 Hz), 0.94 (t, 3H, J = 7.3 Hz), 0.84 (t, 6H, J = 7.4 Hz).

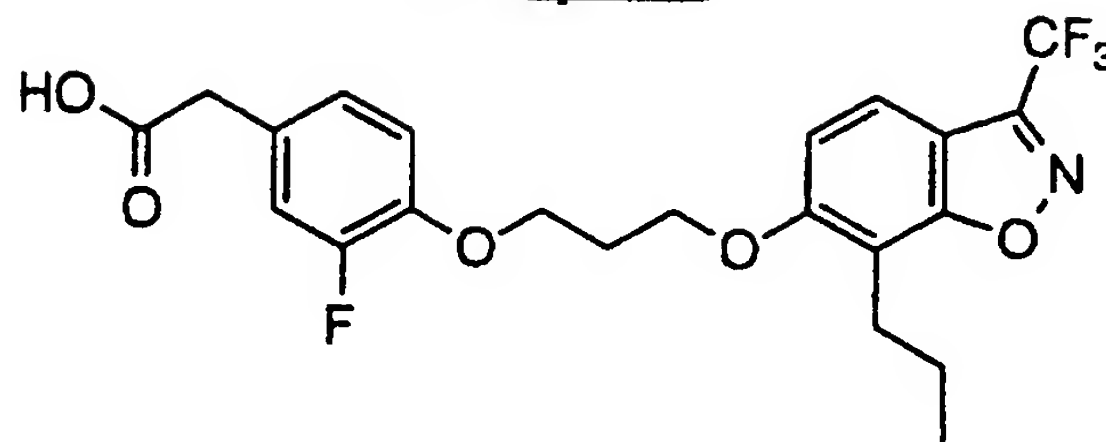
Step E: Preparation of 3,5-dipropyl-4-(3-(3-ethyl-7-propyl-6-benz-[4,5]-isoxazoloxy)-propyloxy)phenylacetic acid

Using the method of Example 18, methyl 3,5-dipropyl-4-(3-(3-ethyl-7-propyl-6-benz-[4,5]-isoxazoloxy)-propyloxy)phenylacetate as the starting material, the title compound was obtained.

¹H NMR(400MHz, CDCl₃): δ 7.39 (d, 1H, J = 8.5 Hz), 6.94 (d, 1H, J = 8.6 Hz), 6.90 (m, 2H), 4.31 (t, 2H, J = 5.9 Hz), 3.94 (t, 2H, J = 5.9 Hz), 3.51 (s, 2H), 2.95 (quart, 2H, J = 7.5 Hz), 2.85 (t, 2H, J = 7.3 Hz), 2.52 (m, 4H), 2.28 (quint, J = 6.5 Hz), 1.71-1.52 (m, 6H), 1.40 (t, 3H, J = 7.3 Hz), 0.94 (t, 3H, J = 7.3 Hz), 0.84 (t, 6H, J = 7.4 Hz).

ESI: MS m/e = 482 (M+1)

- 110 -

Example 42

3-fluoro-4-(3-(7-propyl-3-trifluoromethyl-6-benz-[4, 5]isoxazoloxy)-propyloxy)phenylacetic acid

STEP A: Preparation of Methyl 3-fluoro-4-(3- bromopropoxy)-phenylacetate

A solution of methyl 3-fluoro-4-hydroxyphenylacetate (25.545 grams) in 2-butanone (300 mL) was treated with 1,3-dibromopropane (48.79 mL) and potassium carbonate (50.859 grams). The mixture was refluxed for 4 hours. The reaction mixture was partitioned between isopropyl acetate and pH 4 buffer. The organic was washed once with water, then dried over magnesium sulfate. The organic was filtered and evaporated to an oil which was chromatographed over silica gel with hexane/methylene chloride (2:1) to afford the title compound. This compound was taken forward without further purification.

STEP B: Preparation of 3-trifluoromethyl-7-propyl-6-hydroxybenz-[4, 5]-isoxazole

Using the method and materials in example 20 steps A and B the titled compound was obtained.

STEP C: Preparation of Methyl 3-fluoro-4-(3-(7-propyl-3-trifluoromethyl-6-benz-[4, 5]-isoxazoloxy)propyloxy)phenylacetate

Using the method in example 17 step D substituting methyl 3-fluoro-4-(3-bromopropoxy)phenylacetate and 3-trifluoromethyl-7-propyl-6-hydroxybez-[4, 5]-isoxazole as the starting materials, the titled compound was obtained.

- 111 -

NMR (CDCl₃) δ 7.54 (d, 1H, J = 8.79 Hz); 7.07 (d, 1H, J = 8.83 Hz); 7.02 (d, 1H, J = 10.25 Hz); 6.92 (m, 2H); 4.29 (t, 2H, J = 5.97 Hz); 4.23 (t, 2H, J = 5.98 Hz); 3.67 (s, 1H); 3.53 (s, 2H); 2.88 (t, 2H, J = 7.49 Hz); 2.33 (m, 2H, J = 6.03 Hz); 1.65 (m, 2H); 0.91 (t, 3H, J = 7.41 Hz).

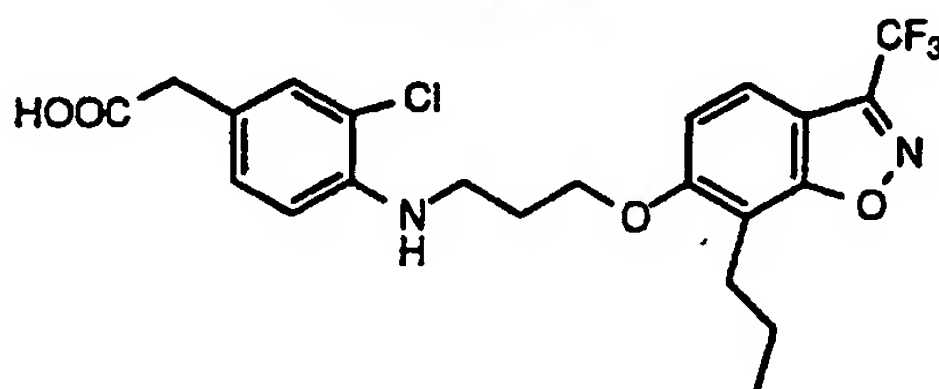
STEP D: Preparation of 3-fluoro-4-(3-(7-propyl-3-trifluoromethyl-6-benz-[4, 5]-isoxazoloxy)propyloxy)phenylacetic acid

Using the method in example 2 step A, substituting Methyl 3-fluoro-4-(3-(7-propyl-3-trifluoromethyl-6-benz-[4, 5]-isoxazoloxy)propyloxy)phenylacetate as the starting material, the titled compound was obtained.

NMR (CDCl₃) δ 7.53 (d, 1H, J = 8.42 Hz); 7.07 (d, 1H, J = 8.82 Hz); 7.01 (d, 1H, J = 10.18 Hz); 6.93 (m, 2H); 4.29 (t, 2H, J = 5.94 Hz); 4.23 (t, 2H, J = 6.06 Hz); 3.56 (s, 2H); 2.87 (t, 2H, J = 7.40 Hz); 2.33 (m, 2H, J = 5.98 Hz); 1.66 (m, 2H); 0.91 (t, 3H, J = 7.41 Hz).

ESI: Mass spec: m/e = 456 (M+1).

Example 43



3-chloro-4-(3-(3-trifluoromethyl-7-propyl-6-benz-[4, 5]-isoxazoloxy)propylamino)phenylacetic acid

STEP A: Preparation of 3-trifluoromethyl-7-propyl-6-hydroxybenz-[4, 5]-isoxazole

Using the method and materials in example 20 steps A and B the titled compound was obtained.

STEP B: Preparation of Methyl 3-chloro-4-(3-bromopropylamino)-phenylacetate

- 112 -

Magnesium oxide (10 grams, 250 mmoles), was added to a solution of 1,3-dibromopropane (139 grams, 70 mL, 700 mmoles) in dimethylacetamide (150 mL). A solution of methyl 3-chloro-4-aminophenylacetate·HCl (23.6 grams, 100 mmoles) in dimethylacetamide (200 mL) was added dropwise over 30 minutes and the mixture stirred at 80°C for 6 hours. The cooled mixture was partitioned with methylene chloride and water. The aqueous phase was extracted with methylene chloride and the combined organic phases washed with brine, dried over magnesium sulfate and concentrated *in vacuo* to an oil. The crude product was chromatographed on a silica gel column eluting with hexane:ethyl acetate (9:1). The product was further purified by a second silica gel chromatography in methylene chloride:hexane (2:3) to give the title compound as an oil. NMR, (CDCl₃): δ 2.15 (qnt, 2H); 3.35 (q, 2H); 3.47 (s, 2H); 3.49 (t, 2H); 3.67 (s, 3H); 6.63 (d, 1H); 7.03 (dd, 1H); 7.17 (d, 1H).

STEP C: Methyl 3-chloro-4-(3-(3-trifluoromethyl-7-propyl-6-benz-[4, 5]-isoxazoloxy)propylamino)phenylacetate

Using the method in example 17 step D substituting Methyl 3-chloro-4-(3-bromopropylamino)phenylacetate and 3-trifluoromethyl-7-propyl-6-hydroxybenz-[4, 5]-isoxazole as the starting materials, the titled compound was obtained.

NMR (CDCl₃) δ 7.54 (d, 1H, J = 8.10 Hz); 7.18 (s, 1H); 7.03 (m, 2H); 6.64 (d, 1H, J = 8.34 Hz); 4.39 (bs, 1H); 4.20 (t, 2H, J = 5.86 Hz); 3.66 (s, 3H); 3.47 (s, 2H); 3.42 (t, 2H, J = 6.83 Hz); 2.92 (t, 2H, J = 7.58 Hz); 2.18 (m, 2H); 1.69 (m, 2H); 0.95 (t, 3H, J = 7.41 Hz).

STEP D: 3-chloro-4-(3-(3-trifluoromethyl-7-propyl-6-benz-[4, 5]-isoxazoloxy)propylamino)phenylacetic acid

A solution of Methyl 3-chloro-4-(3-(3-trifluoromethyl-7-propyl-6-benz-[4, 5]-isoxazoloxy)propylamino)-phenylacetate (Step C, 0.113 grams) in methanol (1.5 mL) was treated with a solution of lithium hydroxide in water (1.01 M; 0.362 mL). The reaction was refluxed 1 hour. The reaction mixture was partitioned between

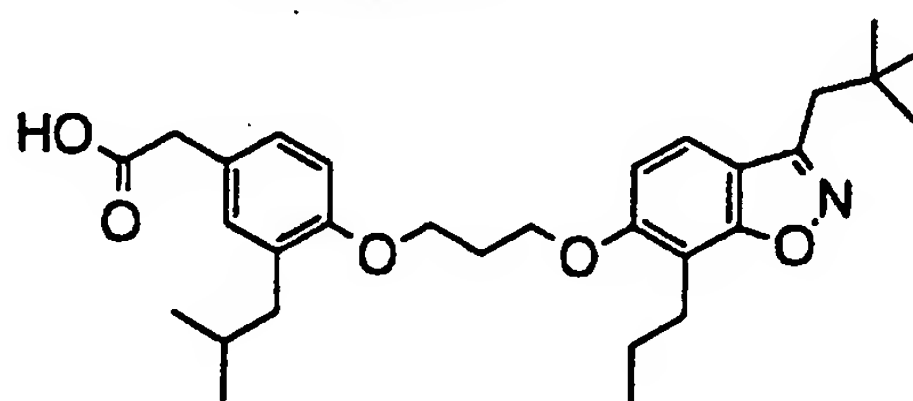
- 113 -

isopropyl acetate and 0.1N HCl. The organic was dried over magnesium sulfate, filtered and concentrated to a solid. The solid was suspended in methylene chloride/cyclohexane (1:1; 2 mL). The mixture was refluxed briefly and cooled to 0°C. The title compound was isolated by filtration..

NMR (CDCl₃) δ 7.54 (d, 1H, J = 8.10 Hz); 7.18 (s, 1H); 7.03 (m, 2H); 6.64 (d, 1H, J = 8.34 Hz); 4.19 (t, 2H, J = 5.86 Hz); 3.50 (s, 2H); 3.43 (t, 2H, J = 6.83 Hz); 2.92 (t, 2H, J = 7.58 Hz); 2.18 (m, 2H); 1.69 (m, 2H); 0.95 (t, 3H, J = 7.41 Hz).

ESI: Mass spec: m/e = 471 (M+1).

Example 44



3-Isobutyl-4-(3-(3-neo-pental-7-propyl-6-benz-[4,5]-isoxazoloxy)-propyloxy)phenylacetic acid

Step A: Preparation of methyl 4-methallyloxyphenylacetate

Using the method of Example 17, step A, methallyl bromide as the starting material, the title compound was obtained.

¹H NMR (400MHz, CDCl₃): δ 7.16 (d, 2H, J = 8.5 Hz), 6.86 (dd, 2H, J = 8.6, 2.1 Hz), 5.06 (s, 1H), 4.97 (s, 1H), 4.39 (s, 2H), 3.66 (s, 3H), 3.54 (s, 2H), 1.80 (s, 3H).

Step B: Preparation of methyl 4-hydroxy-3-methallylphenylacetate

Using the method of Example 17, step B, methyl 4-methallyloxyphenylacetate as the starting material, the title compound was obtained.

¹H NMR (400MHz, CDCl₃): δ 7.03 (dd, 1H, J = 8.1, 2.2 Hz), 6.98 (d, 1H, J = 2.5 Hz), 6.98 (d, 1H, J = 8.2 Hz), 5.18 (s, 1H), 4.90 (s, 1H), 4.82 (s, 1H), 3.66 (s, 3H), 3.52 (s, 2H), 3.33 (s, 2H).

- 114 -

Step C: Preparation of methyl 4-hydroxy-3-isobutylphenylacetate

Using the method of Example 17, step C, methallyl bromide as the starting material, the title compound was obtained.

^1H NMR(400MHz, CDCl_3): δ 6.95 (m, 2H), 6.66 (d, 2H, $J = 8.2$ Hz), 3.70 (s, 3H), 3.54 (s, 2H), 2.43 (d, 2H, $J = 7.5$ Hz), 1.91 (m, 1H), 0.92 (d, 6H, $J = 7.6$ Hz).

Step D: Preparation of methyl 3-isobutyl-4-(3-(3-neo-pental-7-propyl-6-benz-[4,5]-isoxazoloxy)-propyloxy)phenylacetate

Using the method of Example 17, step D, methyl 4-hydroxy-3-isobutylphenylacetate and 1-bromo-3-(3-neo-pental-7-propyl-6-benz-[4,5]-isoxazoloxy)phenoxyp propane as the starting material, the title compound was obtained.

^1H NMR(400MHz, CDCl_3): δ 7.34 (d, 1H, $J = 8.7$ Hz), 7.04 (dd, 1H, $J = 8.3, 2.2$ Hz), 6.97 (d, 1H, $J = 2.2$ Hz), 6.90 (d, 1H, $J = 8.7$ Hz), 6.78 (d, 1H, $J = 8.2$ Hz), 4.24 (t, 2H, $J = 6.1$ Hz), 4.14 (t, 2H, $J = 5.9$ Hz), 3.66 (s, 3H), 3.51 (s, 2H), 2.83 (t, 2H, $J = 7.4$ Hz), 2.78 (s, 2H), 2.42 (d, 2H, $J = 7.0$ Hz), 2.30 (quint, 2H, $J = 6.0$ Hz), 1.83 (m, 1H), 1.64 (m, 2H), 1.02 (s, 9H), 0.91 (t, 3H, $J = 7.4$ Hz), 0.82 (d, 6H, $J = 6.7$ Hz).

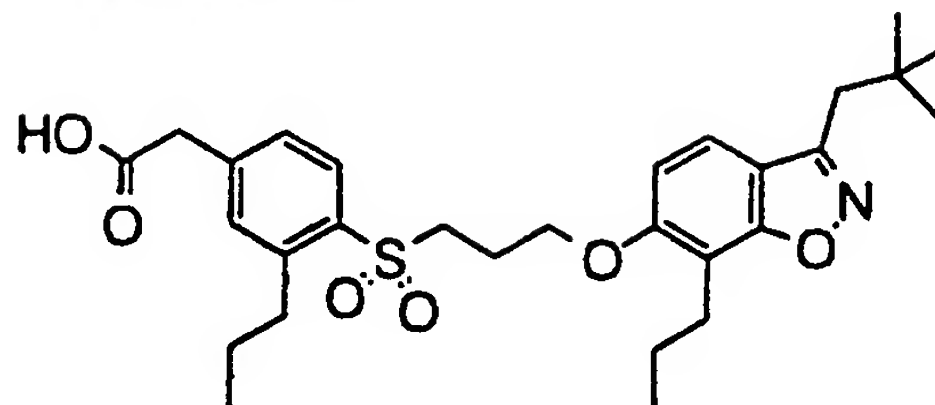
Step E: Preparation of 3-isobutyl-4-(3-(3-neo-pental-7-propyl-6-benz-[4,5]-isoxazoloxy)-propyloxy)phenylacetic acid

Using the method of Example 18, the product of step D was saponified to give the title compound.

^1H NMR(400MHz, CDCl_3): δ 7.34 (d, 1H, $J = 8.7$ Hz), 7.04 (dd, 1H, $J = 8.3, 2.2$ Hz), 6.97 (d, 1H, $J = 2.2$ Hz), 6.90 (d, 1H, $J = 8.7$ Hz), 6.78 (d, 1H, $J = 8.2$ Hz), 4.24 (t, 2H, $J = 6.1$ Hz), 4.14 (t, 2H, $J = 5.9$ Hz), 3.51 (s, 2H), 2.83 (t, 2H, $J = 7.4$ Hz), 2.78 (s, 2H), 2.42 (d, 2H, $J = 7.0$ Hz), 2.30 (quint, 2H, $J = 6.0$ Hz), 1.83 (m, 1H), 1.64 (m, 2H), 1.02 (s, 9H), 0.91 (t, 3H, $J = 7.4$ Hz), 0.82 (d, 6H, $J = 6.7$ Hz).

ESI: MS $m/e = 496$ ($M+1$)

- 115 -

Example 45

3-Propyl-4-(3-(3-neo-pental-7-propyl-6-benz-[4,5]-isoxazoloxy)propylthio)phenylacetic acid S,S-dioxide

Step A: Preparation of methyl 3-propyl-4-(3-(3-neo-pental-7-propyl-6-benz-[4,5]-isoxazoloxy)propylthio)phenylacetate S,S-dioxide

Using the method of Example 13, methyl 3-propyl-4-(3-(3-neo-pental-7-propyl-6-benz-[4,5]-isoxazoloxy)propylthio)phenylacetate as the starting material, the title compound was obtained.

^1H NMR (400MHz, CDCl_3): δ 7.96 (d, 1H, $J = 8.6$ Hz), 7.33 (d, 1H, $J = 8.6$ Hz), 7.32 (m, 2H), 6.92 (d, 1H, $J = 8.7$ Hz), 4.12 (t, 2H, $J = 5.9$ Hz), 3.69 (s, 3H), 3.66 (s, 2H), 3.35 (t, 2H, $J = 7.5$ Hz), 2.94 (t, 2H, $J = 7.9$ Hz), 2.78 (2H, $J = 8.0$ Hz), 2.27 (m, 2H), 1.74-1.58 (m, 4H), 1.02 (s, 9H), 0.98 (t, 3H, $J = 7.4$ Hz), 0.98 (t, 3H, $J = 7.3$ Hz)

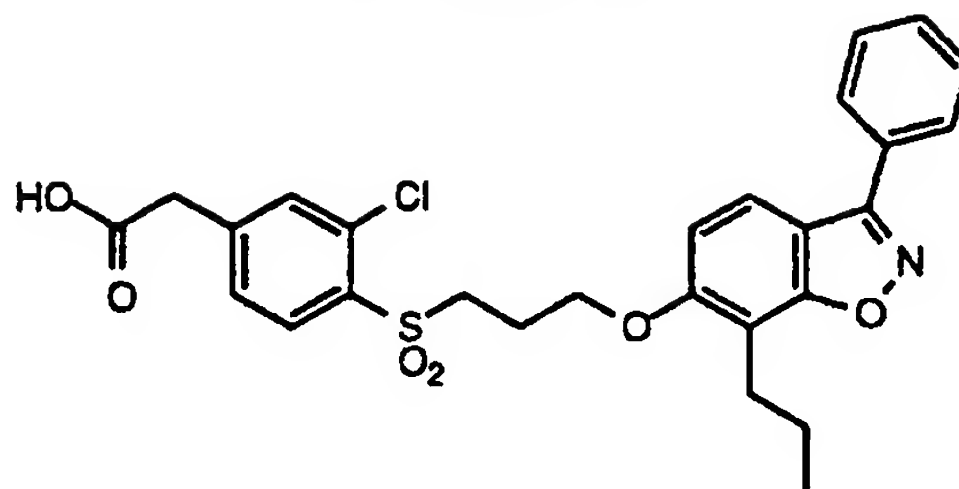
Step B: Preparation of 3-propyl-4-(3-(3-neo-pental-7-propyl-6-benz-[4,5]-isoxazoloxy)propylthio)phenylacetic acid S,S-dioxide

Using the method of Example 14, methyl 3-propyl-4-(3-(3-neo-pental-7-propyl-6-benz-[4,5]-isoxazoloxy)propylthio)phenylacetate S,S-dioxide as the starting material, the title compound was obtained.

^1H NMR (400MHz, CDCl_3): δ 7.96 (d, 1H, $J = 8.6$ Hz), 7.33 (d, 1H, $J = 8.6$ Hz), 7.32 (m, 2H), 6.92 (d, 1H, $J = 8.7$ Hz), 4.12 (t, 2H, $J = 5.9$ Hz), 3.66 (s, 2H), 3.35 (t, 2H, $J = 7.5$ Hz), 2.94 (t, 2H, $J = 7.9$ Hz), 2.78 (2H, $J = 8.0$ Hz), 2.27 (m, 2H), 1.74-1.58 (m, 4H), 1.02 (s, 9H), 0.98 (t, 3H, $J = 7.4$ Hz), 0.98 (t, 3H, $J = 7.3$ Hz)

ESI: MS $m/e = 530$ ($M+1$)

- 116 -

Example 46

-Chloro-4-(3-(3-phenyl-7-propyl-6-benz-[4,5]-isoxazoloxy)-propylsulfoxy)phenylacetic acid

Step 1

The acid prepared in Example 16 Step 5 (19.2 mg, 1.0 Eq, 0.04 mmol) was dissolved in methylene chloride (0.3 ml) with mCPBA (85%, 18.2 mg, 2.3 Eq, 0.11 mmol). At 1 1/4 Hr the mixture was diluted with EtOAc and sodium bisulfite 10% aq. The EtOAc extract was washed again with sodium bisulfite 10% aq, followed by NaCl sat'd aq. The EtOAc extracts were dried over MgSO₄ and reduced to an oil *i. vac.*

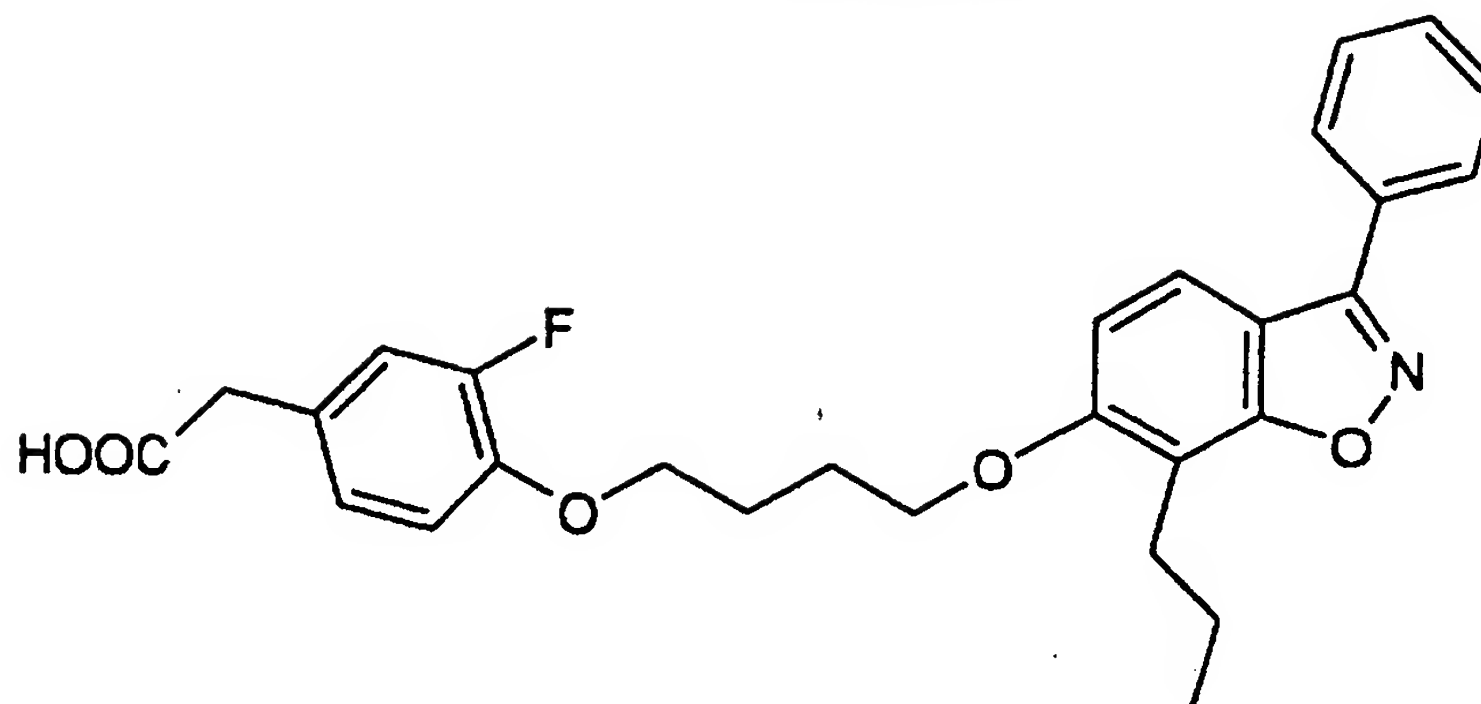
The product was purified by elution from a reversed phase RP-8 col (E. Merck 40-63 μ) with 65 : 35 CH₃CN : H₂O 0.1 % TFA. The ester is obtained as a glass.

Analytical HPLC 75 : 25 CH₃CN : H₂O 0.1 % TFA, E. Merck RP-8 5 μ 4 X 250 mm, 1 ml/min. UV 210, RT 7.73 min.

Characteristic NMR Resonances; ¹H NMR 400MHz (CDCl₃); 8.09 (d, 1H, J = 8.1 Hz), 7.90 (m, 1H), 7.62 (d, 1H, J = 8.7 Hz), 7.52 (m, 4H), 7.38 (dd, 1H, J = 8.2, 1.6 Hz), 6.89 (d, 1H, J = 8.8 Hz), 4.17 (t, 2H, J = 5.8 Hz), 3.70 (s, 2H), 3.67 (m, 2H), 2.87 (t, 2H, J = 7.4 Hz), 2.28 (m, 2H), 1.67 (sext, 2 H, 7.5 Hz), 0.93 (t, 3H, J = 7.36 Hz).

MS ESI M+1 = 528.3. MW = 527.1

- 117 -

Example 47

3-fluoro-4-(4-(3-phenyl-7-propyl-6-benz-[4, 5]-isoxazoloxy)-butyloxy)phenylacetic acid

STEP A: Preparation of Methyl 3-fluoro-4-(4-bromobutyloxy)-phenylacetate

A solution of methyl 3-fluoro-4-hydroxyphenylacetate and 1,4-dibromobutane (Step A; 0.552 grams) in 2-butanone (6 mL) was treated with 3-propyl-2,4-dihydroxypropiophenone (0.299 grams). Potassium carbonate (0.217 grams) was added and the mixture refluxed for 4 hours. The reaction was partitioned between isopropyl acetate and pH 4 phosphate buffer. The organic was dried over magnesium sulfate, filtered and evaporated to a residue which was chromatographed over silica gel to give the product.

NMR (CDCl₃) δ 7.08 (d, 1H); 6.91 (m, 2H); 4.05 (t, 2H); 3.69 (s, 3H); 3.52 (s, 2H); 3.48 (t, 2H); 2.06 (m, 2H); 1.97 (m, 2H).

STEP B: Preparation of 3-phenyl-7-propyl-6-hydroxybenz-[4, 5]-isoxazole

Using the method and materials in example 16 steps 1A, 1, 2, and 3 the titled compound was obtained.

STEP C: Preparation of Methyl 3-fluoro-4-(4-(3-phenyl-7-propyl-6-benz-[4, 5]-isoxazoloxy)butyloxy)phenylacetate

- 118 -

Using the method in example 23 step 3 substituting Methyl 3-fluoro-4-(4-bromobutyloxy)phenylacetate as the starting material, the titled compound was obtained.

NMR (CDCl₃) δ 7.92 (m, 2H); 7.64 (d, 1H, J = 8.70 Hz); 7.51 (m, 3H); 6.97 (m, 4H); 4.12 (m, 4H); 3.67 (s, 3H); 3.53 (s, 2H); 2.90 (t, 2H, J = 7.35 Hz); 2.02 (m, 4H); 1.71 (m, 2H); 0.96 (t, 3H, J = 7.36 Hz).

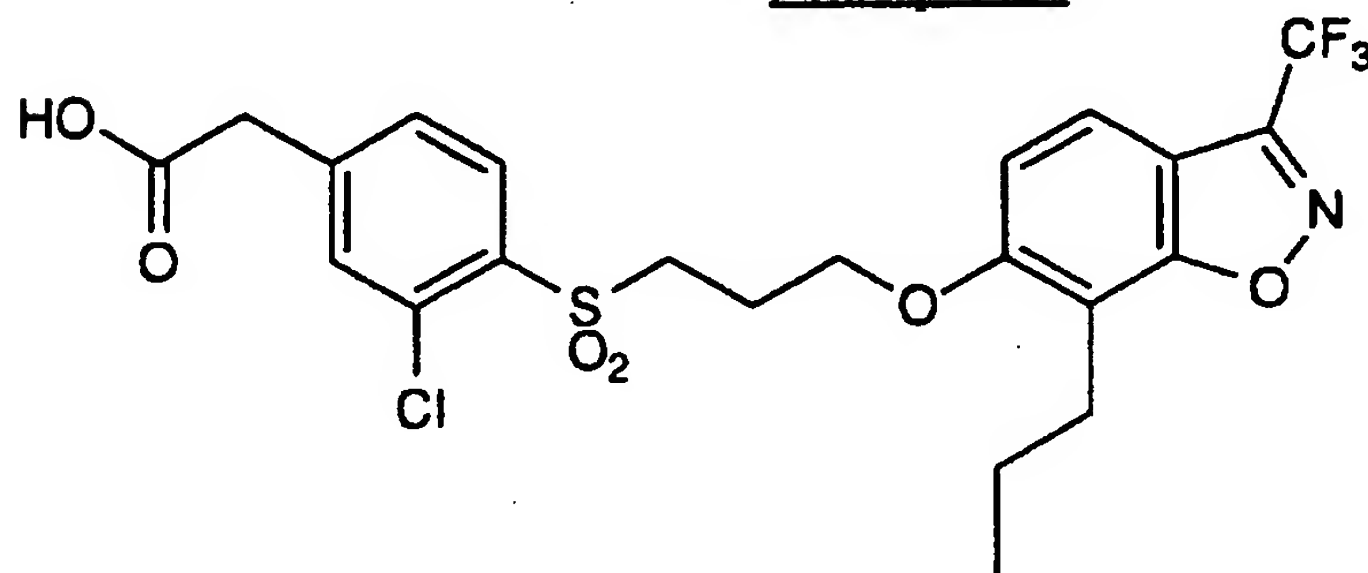
STEP D: Preparation of 3-fluoro-4-(4-(3-phenyl-7-propyl-6-benz-[4, 5]-isoxazoloxy)butyloxy)phenylacetic acid

Using the method in example 23 step 4 substituting Methyl 3-fluoro-4-(4-(3-phenyl-7-propyl-6-benz-[4, 5]-isoxazoloxy)butyloxy)-phenylacetate as the starting material, the titled compound was obtained.

NMR (CDCl₃) δ 7.93 (m, 2H); 7.65 (d, 1H, J = 8.70 Hz); 7.51 (m, 3H); 6.98 (m, 4H); 4.12 (m, 4H); 3.58 (s, 2H); 2.90 (t, 2H, J = 7.35 Hz); 2.02 (m, 4H); 1.71 (m, 2H); 0.99 (t, 3H, J = 7.36 Hz).

ESI: Mass spec: m/e = 479 (M+1).

Example 48



3-chloro-4-(3-(7-propyl-3-trifluoromethyl-6-benz-[4, 5]-isoxazoloxy)propyl-thio)phenylacetic acid S, S-dioxide

STEP A: Preparation of Methyl 3-chloro-4-(3-(7-propyl-3-trifluoromethyl-6-benz-[4, 5]-isoxazoloxy)propyl-thio)phenylacetate

Using the method and materials in example 20 step A, B and C the titled compound was obtained.

- 119 -

STEP B: Preparation of Methyl 3-chloro-4-(3-(7-propyl-3-trifluoromethyl-6-benz-[4, 5]-isoxazoloxy)propyl-thio)phenylacetate S, S-dioxide

Using the method in example 13 substituting Methyl 3-chloro-4-(3-(7-propyl-3-trifluoromethyl-6-benz-[4, 5]-isoxazoloxy)propyl-thio)phenylacetate as the starting material and using 2 equivalents of the oxidating agent, the titled compound was obtained. This compound was filtered through a pad of silica gel using ethyl ether and hexane (1:1) as the mobile phase, and taken forward without further purification.

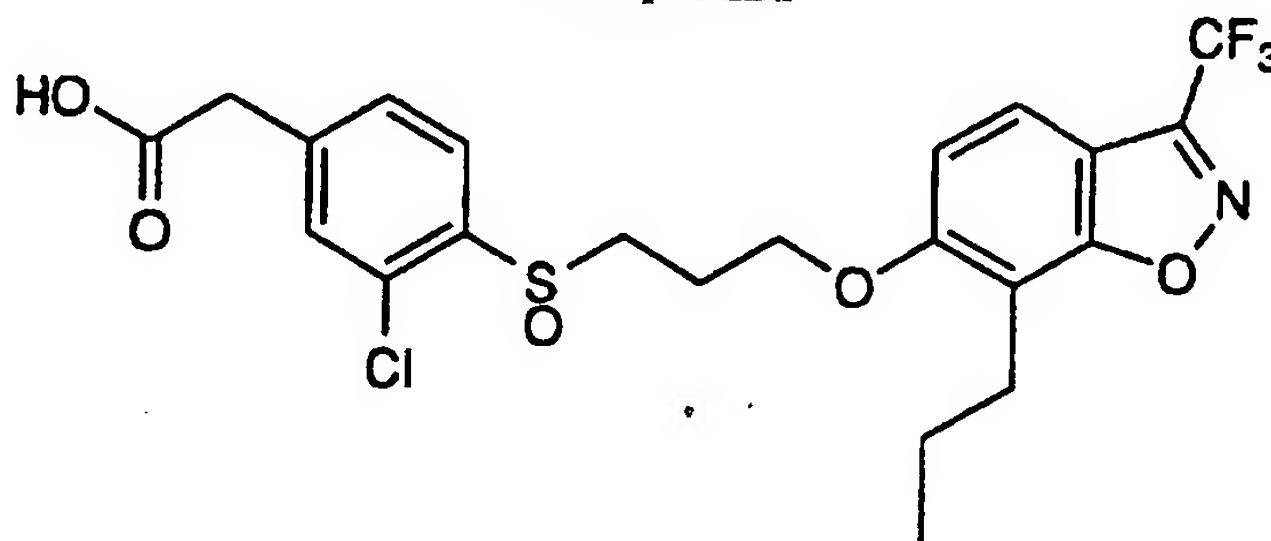
STEP C: Preparation of 3-chloro-4-(3-(7-propyl-3-trifluoromethyl-6-benz-[4, 5]-isoxazoloxy)propyl-thio)phenylacetic acid S, S-dioxide

Using the method in example 2 step A, substituting Methyl 3-chloro-4-(3-(7-propyl-3-trifluoromethyl-6-benz-[4, 5]-isoxazoloxy)propyl-thio)phenylacetate S, S-dioxide as the starting material, the titled compound was obtained.

NMR (CDCl₃) δ 8.09 (d, 1H, J = 8.15 Hz); 7.51 (m, 2H); 7.39 (d, 1H, J = 5.38 Hz); 6.97 (d, 1H, J = 8.87 Hz); 4.18 (t, 2H, J = 5.86 Hz); 3.71 (s, 2H); 3.64 (t, 2H, J = 7.49 Hz); 2.85 (t, 2H, J = 7.41 Hz); 2.30 (m, 2H); 1.64 (m, 2H); 0.91 (t, 3H, J = 7.36 Hz).

ESI: Mass spec: m/e = 520 (M+1).

Example 49



3-chloro-4-(3-(7-propyl-3-trifluoromethyl-6-benz-[4, 5]-isoxazoloxy)propyl-thio)phenylacetic acid S-oxide

- 120 -

STEP A: Preparation of Methyl 3-chloro-4-(3-(7-propyl-3-trifluoromethyl-6-benz-[4, 5]-isoxazoloxy)propyl-thio)phenylacetate S-oxide

Using the method in example 11 substituting Methyl 3-chloro-4-(3-(7-propyl-3-trifluoromethyl-6-benz-[4, 5]-isoxazoloxy)propyl-thio)phenylacetate as the starting material, (Example 20, step C) the titled compound was obtained. This compound was filtered through a pad of silica gel using ethyl ether and hexane (1:1) as the mobile phase, and taken forward without further purification.

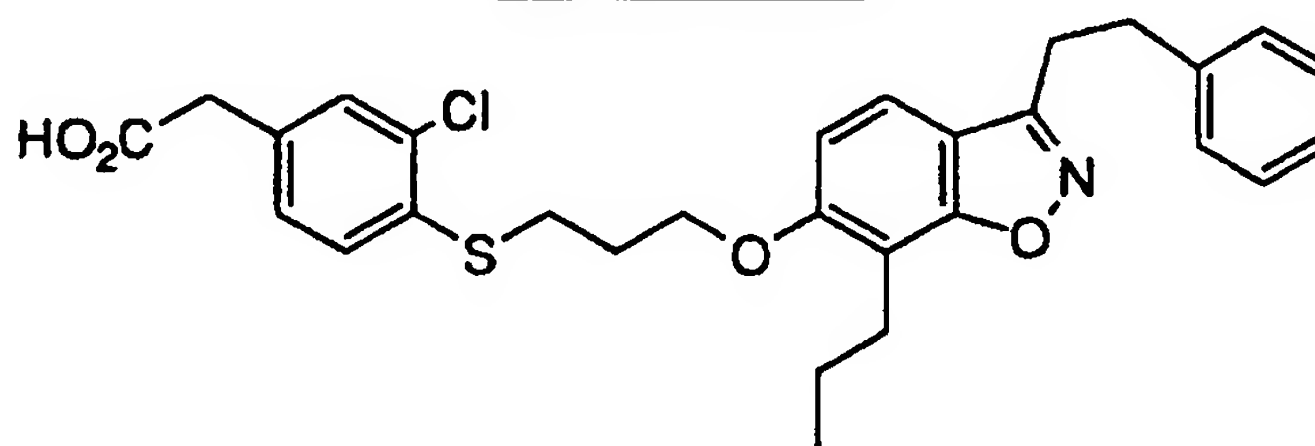
STEP B: Preparation of 3-chloro-4-(3-(7-propyl-3-trifluoromethyl-6-benz-[4, 5]-isoxazoloxy)propyl-thio)phenylacetic acid S-oxide

Using the method in example 2 substituting Methyl 3-chloro-4-(3-(7-propyl-3-trifluoromethyl-6-benz-[4, 5]-isoxazoloxy)propyl-thio)phenylacetate S-oxide as the starting material, the titled compound was obtained.

NMR (CDCl₃) δ 7.85 (d, 1H, J = 8.02 Hz); 7.52 (d, 2H, J = 8.79 Hz); 7.43 (d, 1H, J = 6.43 Hz); 7.35 (s, 1H); 6.99 (d, 1H, J = 8.87 Hz); 4.18 (m, 2H); 3.68 (s, 2H); 3.38 (m, 1H); 3.02 (m, 1H); 2.84 (t, 2H, J = 7.49 Hz); 2.44 (m, 1H); 2.18 (m, 1H); 1.63 (m, 2H); 0.91 (m, 3H).

ESI: Mass spec: m/e = 504 (M+1).

EXAMPLE 50



3-chloro-4-(3-(2-phenylethyl)-7-propyl-6-benz[4,5]isoxazoloxy)propyl-thio)phenylacetic acid

Step A Preparation of 1,3-dihydroxy-4-(3-phenylpropionyl)-2-(n-propyl)benzene

- 121 -

Using the procedure in Example 51, step 1, 3-phenylpropionic acid and 2-(n-propyl)resorcinol were condensed in triflic acid to form 1,3-dihydroxy-4-(3-phenylpropionyl)-2-(n-propyl)benzene.

NMR (CDCl₃): d 7.20 (d, 1H); 7.19 - 7.33 (m, 5H); 6.33 (d, 1H); 5.28 (s, 1H); 3.24 (t, 2H); 3.04 (t, 2H); 2.63 (t, 2H); 1.57 (m, 2H); 0.99 (t, 3H).

Step B Preparation of 6-hydroxy-3-(2-phenylethyl)-7-(n-propyl)benz-[4,5]isoxazole

Using the procedures in Example 51, steps 2 and 3, 1,3-dihydroxy-4-(3-phenylpropionyl)-2-(n-propyl)benzene was converted into 6-hydroxy-3-(2-phenylethyl)-7-(n-propyl)benz[4,5]isoxazole.

NMR (CDCl₃): d 7.21 - 7.32 (m, 5H); 7.18 (d, 1H); 6.77 (d, 1H); 5.32 (vbs, 1H); 3.22 (m, 2H); 3.14 (m, 2H); 2.77 (t, 2H); 1.74 (m, 2H); 1.00 (t, 3H).

Step C Preparation of methyl 3-chloro-4-(3-(2-phenylethyl)-7-propyl-6-benz[4,5]isoxazoloxy)propylthio)phenylacetate

Using the procedure in Example 16, step 4, 6-hydroxy-3-(2-phenylethyl)-7-(n-propyl)benz[4,5]isoxazole and methyl 3-chloro-4-(3-bromopropylthio)phenylacetate were heated in DMF with Cs₂CO₃ to prepare methyl 3-chloro-4-(3-(2-phenylethyl)-7-propyl-6-benz[4,5]-isoxazoloxy)propylthio)phenylacetate.

NMR (CDCl₃): d 7.21 - 7.35 (m, 8H); 7.13 (dd, 1H); 6.87 (d, 1H); 4.19 (t, 2H); 3.71 (s, 3H); 3.57 (s, 2H); 3.12 - 3.27 (m, 6H); 2.88 (t, 2H); 2.20 (m, 2H), 1.70 (m, 2H); 0.95 (t, 3H).

Step D Preparation of 3-chloro-4-(3-(2-phenylethyl)-7-propyl-6-benz[4,5]isoxazoloxy)propylthio)phenylacetic acid

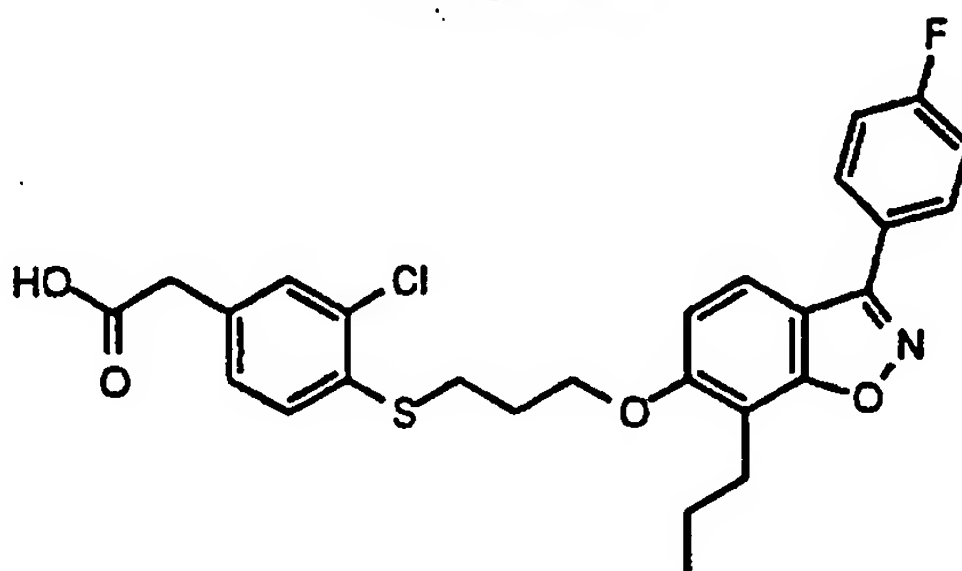
Using the procedure in Example 2, methyl 3-chloro-4-(3-(2-phenylethyl)-7-propyl-6-benz[4,5]isoxazoloxy)propylthio)phenylacetate was saponified with LiOH to form 3-chloro-4-(3-(2-

- 122 -

phenylethyl)-7-propyl-6-benz[4,5]isoxazoloxy)propylthio)phenylacetic acid.

NMR (CDCl₃): d 7.21 - 7.35 (m, 8H); 7.13 (dd, 1H); 6.87 (d, 1H); 4.19 (t, 2H); 3.60 (s, 2H); 3.12 - 3.26 (m, 6H); 2.88 (t, 2H), 2.20 (m, 2H); 1.69 (m, 2H); 0.95 (t, 3H)

Example 51



3-Chloro-4-(3-(3-(4-fluorophenyl)-7-propyl-6-benz-[4,5]-isoxazoloxy)-propylthio)phenylacetic acid

Step 1

Commercially available 2-propylresorcinol (3.0 g, 1.0 Eq, 0.019 mol) and p-fluorobenzoic acid (3.2 g, 1.15 Eq, 0.023 mol) were dissolved in trifluoromethanesulfonic acid (10 ml) at RT. The mixture was heated to 85 C under N₂. At 2 1/2 hrs, the reaction was cooled to RT and poured into H₂O. The mixture was extracted with EtOAc. The extracts were washed with NaHCO₃ sat'd. aq., washed with NaCl aq sat'd, and dried over MgSO₄. The EtOAc solution was reduced *i. vac*. The product was purified by elution from a silica gel column (20 g E. Merck 40-63 μ) with toluene : EtOAc 98 : 2.

Characteristic NMR Resonances; ¹H NMR 400MHz (CDCl₃); 7.64 (m, 2H), 7.30 (d, 1H, J = 8.8 Hz), 7.15 (m, 2H), 6.31 (d, 2H, J = 8.8 Hz), 5.47 (s, 1H), 2.66 (dd, 2H, J = 9.3, 7.6 Hz), 1.60 (m, 2H), 0.99 (t, 3H). MS ESI M+1 = 275.1. MW = 274.1

- 123 -

Step 2

The ketone of Example 52 step 1 (2.5 g, 1.0 Eq, 9.1 mmol) was converted to the oxime with $\text{NH}_2\text{OH}\cdot\text{HCl}$ (2.54 g, 4.0 Eq, 37 mmol) as for the procedure of Example 7 Step A. The product was purified by recrystallization from toluene to provide one isomer.

Characteristic NMR Resonances; ^1H NMR 400MHz (CDCl_3); 7.27 (m, 2H), 7.17 (m, 2H), 6.50 (d, 1H, $J = 8.7$ Hz), 6.21 (d, 1H, $J = 8.7$ Hz), 2.66 (dd, 2H, $J = 9.3, 7.6$ Hz), 1.61 (sext, 2H, $J = 7.7$ Hz), 0.99 (t, 3H, $J = 7.4$ Hz).

MS ESI $M+1 = 290$. MW = 289.

Step 3

The oxime of Example 51 step 2 (1.45 g, 5 mmol) was converted to the 3-(p-fluorophenyl)-6-hydroxy-7-propylbenzoxazole as for Example 7 Step A. The product was purified by recrystallization from toluene.

Characteristic NMR Resonances; ^1H NMR 400MHz (CDCl_3); 7.90 (m, 2H), 7.52 (d, 2H, $J = 8.5$ Hz), 7.2 (m, 2H), 6.86 (d, 1H, $J = 8.6$ Hz), 5.14 (s, 1H), 2.90 (dd, 2H, J unresolved), 1.75 (sext, 2H, $J = 7.5$ Hz), 1.01 (t, 3H, $J = 7.3$ Hz).

MS ESI $M+1 = 272.0$. MW = 271.1

Step 4

The 3-(p-fluorophenyl)-6-hydroxy-7-propylbenzoxazole of Example 51 Step 3 (285 mg, 1.0 Eq, 1 mmol) was coupled with the bromide of Example 16 Step 1A (390 mg, 1.1 Eq, 1.1 mmol) as for Example 16 Step 4. The product was purified by elution from a silica gel column (40 g E. Merck 40-63 μ) with toluene : hexanes : EtOAc 70 : 26 : 4.

Characteristic NMR Resonances; ^1H NMR 400MHz (CDCl_3); 7.91 (m, 2H), 7.60 (d, 1H, $J = 8.7$ Hz), 7.26 (m, 4H), 7.11 (dd, 1H, $J = 8.1, 1.8$ Hz), 6.96 (d, 1H, 8.8 Hz), 4.21 (t, 2H, $J = 5.8$ Hz), 3.68 (s, 2H), 3.54 (s, 2H), 3.17 (t, 2H, $J = 7.1$ Hz), 2.91 (dd, 2H, J unresolved), 2.19 (pent, 2H, $J = 5.9$ Hz), 1.71 (sext, 2H, $J = 7.5$ Hz), 0.96 (t, 3H, $J = 7.4$ Hz).

MS ESI $M+1 = 528.3$. MW = 527.1

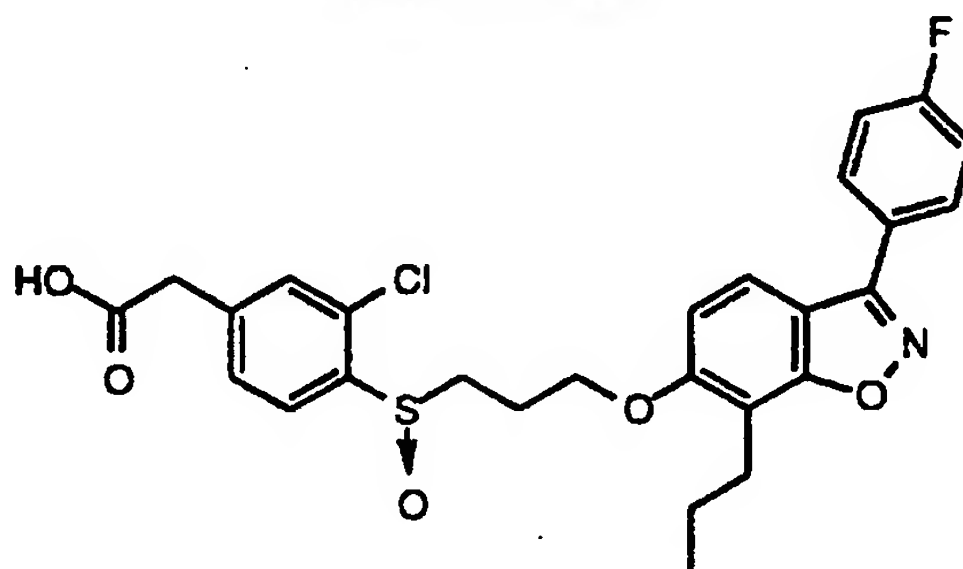
- 124 -

Step 5

The ester of Example 51 Step 4 (344 mg, 1.0 Eq, 0.65 mmol) was hydrolyzed with LiOH (869 μ L, 1.5 N, 2.0 Eq, 1.3 mmol) as described in Example 16 Step 5. The product is purified by recrystallization from MeOH.

Characteristic NMR Resonances; ^1H NMR 400MHz (CDCl_3); 7.89-7.94 (m, 2H), 7.59 (d, 1H, $J = 8.8$ Hz), 7.2-7.5 (m, 4H), 7.11 (dd, 1H, $J = 8.1, 1.9$ Hz), 6.96 (d, 1H, 8.8 Hz), 4.20 (t, 2H, $J = 5.8$ Hz), 3.58 (s, 2H), 3.17 (t, 2H, $J = 7.1$ Hz), 2.91 (t, 2H, $J = 7.6$ Hz), 2.20 (pent, 2H, $J = 6.1$ Hz), 1.70 (sext, 2H, $J = 7.5$ Hz), 0.96 (t, 3H, $J = 7.4$ Hz).

HPLC; 60 : 40 to 85 : 15 $\text{CH}_3\text{CN} : \text{H}_2\text{O}$ 0.1% TFA 25 min linear gradient. E. Merck 5 μ RP-8 4 X 250 mm. RT 16.2 min. UV 210 nM. MS ESI $\text{M}+1 = 514.2$. MW = 513.1

Example 52

3-Chloro-4-(3-(3-(4-fluorophenyl)-7-propyl-6-benz-[4,5]-isoxazoloxy)-propylsulfinyl)phenylacetic acid

Step 1

The ester of Example 51 Step 4 (60 mg, 1.0 Eq, 0.114 mmol) was combined with mCPBA (85%, 33.4 mg, 1.5 Eq, 0.165 mmol) in methylene chloride (0.5 ml) at 0 C. The mixture was stirred at 0 C for 2 Hrs, followed by stirring at RT for 1 1/2 Hrs. The mixture was diluted with EtOAc and sodium thiosulfate ~10% aq. The EtOAc extract was washed again with sodium thiosulfate ~10% aq, followed by NaHCO_3 sat'd. aq. and NaCl sat'd aq. The EtOAc extracts

- 125 -

were dried over MgSO_4 and reduced to an oil *i. vac.* Two products were recovered by elution from a silica gel column (2.5 g E. Merck 40-63 μ) with toluene : EtOAc 91 : 9

Sulfoxide:

Characteristic NMR Resonances; ^1H NMR 400MHz (CDCl_3); 7.8-7.9 (m, 2H), 7.85 (d, 1H, $J = 8.1$ Hz), 7.59 (d, 1H, $J = 8.8$ Hz), 7.42 (dd, 1H, $J = 8.1, 1.8$ Hz), 7.34 (d, 1H, $J = 1.7$ Hz), 7.2 (m, 2H), 6.93 (d, 1H, $J = 8.8$ Hz), 4.15-4.26 (complex m, 2H), 3.70 (s, 3H), 3.65 (s, 2H), 3.33-3.64 (complex m, 1H), 2.97-3.04 (complex m, 1H), 2.86 (dd, 2H, $J = 8.8, 7.5$ Hz), 2.40-2.47 (complex m, 1H), 2.12-2.22 (complex m, 1H), 1.68 (sext, 2H, $J = 7.5$ Hz), 0.933 (t, 3H, $J = 7.4$ Hz).

MS ESI $M+1 = 544$. MW = 543.5

Sulfone:

Characteristic NMR Resonances; ^1H NMR 400MHz (CDCl_3); 8.09 (d, 1H, $J = 8.1$ Hz), 7.9 (m, 2H), 7.58 (d, 1H, $J = 8.7$ Hz), 7.49 (d, 1H, $J = 1.7$ Hz), 7.38 (dd, 1H, $J = 8.1, 1.7$ Hz), 7.14-7.24 (m, 2H), 6.90 (d, 1H, $J = 8.8$ Hz), 4.18 (t, 2H, $J = 5.8$ Hz), 3.71 (s, 3H), 3.67 (s, 2H), 3.66 (t, 2H, J obscured), 2.87 (dd, 2H, $J = 8.6, 7.4$ Hz), 2.30 (m, 2H), 1.67 (sext, 2H, $J = 7.4$ Hz), 0.94 (t, 3H, $J = 7.4$ Hz).

MS ESI $M+1 = 560.4$. MW = 559.5

Step 2

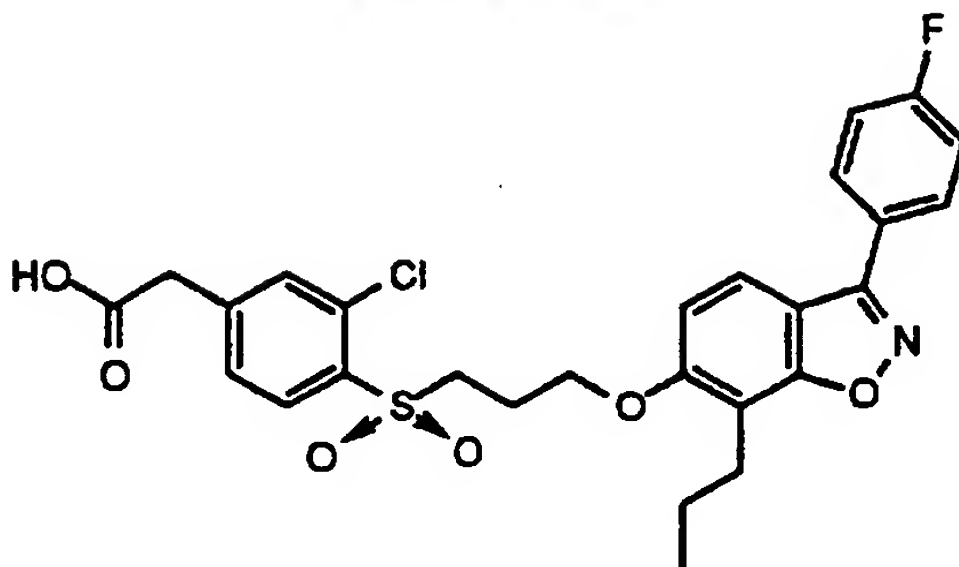
The sulfoxide of Example 52 step 1 (45 mg, 1.0 Eq, 0.083 mmol) was hydrolyzed with LiOH (110 μL , 1.5 N, 2.0 Eq, 0.166 mmol) as described in Example 16 Step 5.

Characteristic NMR Resonances; ^1H NMR 400MHz (CDCl_3); 7.88-7.92 (m, 2H), 7.85 (d, 1H, $J = 8.1$ Hz), 7.58 (d, 1H, $J = 8.7$ Hz), 7.42 (d, 1H, $J = 8.1$ Hz), 7.35 (s, 1H), 7.21 (m, 2H), 6.91 (d, 1H, $J = 8.7$ Hz), 4.1-4.25 (complex m, 2H), 3.67 (s, 2H), 3.35-3.42 (complex m, 1H), 2.99-3.06 (complex m, 1H), 2.85 (t, 2H, $J = 7.4$ Hz), 2.38-2.45 (complex m, 1H), 2.1-2.2 (complex m, 1H), 1.65 (sext, 2H, $J = 7.4$ Hz), 0.916 (t, 3H, $J = 7.3$ Hz).

HPLC; 65 : 35 $\text{CH}_3\text{CN} : \text{H}_2\text{O}$ 0.1% TFA isocratic. E. Merck 5 μ RP-8 4 X 250 mm. RT 7.4 min. UV 210 nm.

- 126 -

MS ESI M+1 = 530.3. MW = 529.1

Example 53

3-Chloro-4-(3-(3-(4-fluorophenyl)-7-propyl-6-benz-[4,5]-isoxazoloxy)-propylsulfonyl) phenylacetic acid

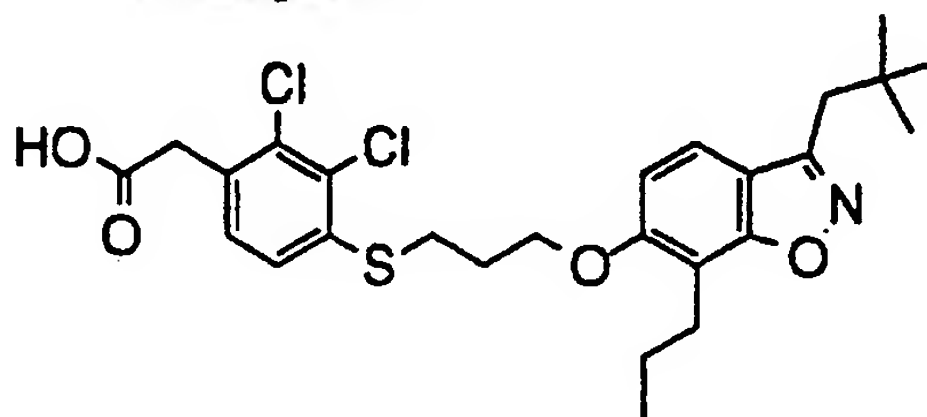
Step 1

The sulfone of Example 52 step 1 (13 mg, 1.0 Eq, 0.023 mmol) was hydrolyzed with LiOH (31 μ L, 1.5 N, 2.0 Eq, 0.046 mmol) as described in Example 16 Step 5.

Characteristic NMR Resonances; ^1H NMR 400MHz (CDCl_3); 8.08 (d, 1H, J = 8.1 Hz), 7.89 (m, 2H), 7.58 (d, 1H, J = 8.7 Hz), 7.49 (d, 1H, J = 1.5 Hz), 7.37 (dd, 1H, J = 8.1, 1.5 Hz), 7.20 (m, 2H), 6.89 (d, 1H, J = 8.8 Hz), 4.17 (t, 2H, J = 5.8 Hz), 3.69 (s, 2H), 3.66 (dd, 2H, J obscured), 2.86 (dd, 2H, J unresolved), 2.25-2.31 (m, 2H), 1.66 (sext, 2H, J = 7.5 Hz), 0.924 (t, 3H, J = 7.4 Hz).

HPLC; 65 : 35 $\text{CH}_3\text{CN} : \text{H}_2\text{O}$ 0.1% TFA isocratic. E. Merck 5 μ RP-8 4 X 250 mm. RT 8.1 min. UV 210 nM.

MS ESI M+1 = 546.3. MW = 545.1

Example 54

- 127 -

2,3-Dichloro-4-(3-(3-neo-pental-7-propyl-6-benz-[4,5]-isoxazoloxy)-propylthio)phenylacetic acid

Step A: Preparation of methyl 2,3-dichloro-4-dimethylcarbamoylthiophenylacetate

A solution of methyl 2,3-dichloro-4-dimethylthiocarbamoyloxyphenylacetate (5.0 g) and in tetramethylene sulfone (65 mL) was heated to reflux for 20 minutes. After 20 minutes, the reaction was cooled as rapidly as possible with a stream of air. The mixture was partitioned between water and ether. The combined organics were washed with water and brine, dried over magnesium sulfate, poured onto a column of silica gel and eluted with ethyl acetate/hexane (20/80) to give the title compound.

^1H NMR (400MHz, CDCl_3): δ 7.49 (d, 1H, $J = 8.3$ Hz), 7.20 (d, 1H, $J = 8.2$ Hz), 3.81 (s, 2H), 3.69 (s, 3H), 3.12 (broad s, 3H), 3.00 (broad s, 3H).

Step B: Preparation of methyl 2,3-dichloro-4-(3-(3-neo-pental-7-propyl-6-benz-[4,5]-isoxazoloxy)propylthio)phenylacetate

Using the method of Example 20, step C, 1-bromo-3-(3-neo-pental-7-propyl-6-benz-[4,5]-isoxazoloxy)phenoxypropane as the starting material, the title compound was obtained.

^1H NMR (300MHz, CDCl_3): δ 7.36 (d, 1H, $J = 8.7$ Hz), 7.17 (d, 1H, $J = 8.3$ Hz), 7.13 (d, 1H, $J = 8.2$ Hz), 6.89 (d, 1H, $J = 8.7$ Hz), 4.19 (t, 2H, $J = 5.8$ Hz), 3.76 (s, 2H), 3.71 (s, 3H), 3.19 (t, 2H, $J = 7.2$ Hz), 2.88 (t, 2H, $J = 7.5$ Hz), 2.81 (s, 2H), 2.22 (quint, 2H, $J = 7.1$ Hz), 1.71 (hex, 2H, $J = 7.3$ Hz), 1.05 (s, 9H), 0.96 (t, 3H, $J = 7.3$ Hz)

Step C: Preparation of 2,3-dichloro-4-(3-(3-neo-pental-7-propyl-6-benz-[4,5]-isoxazoloxy)propylthio)phenylacetic acid

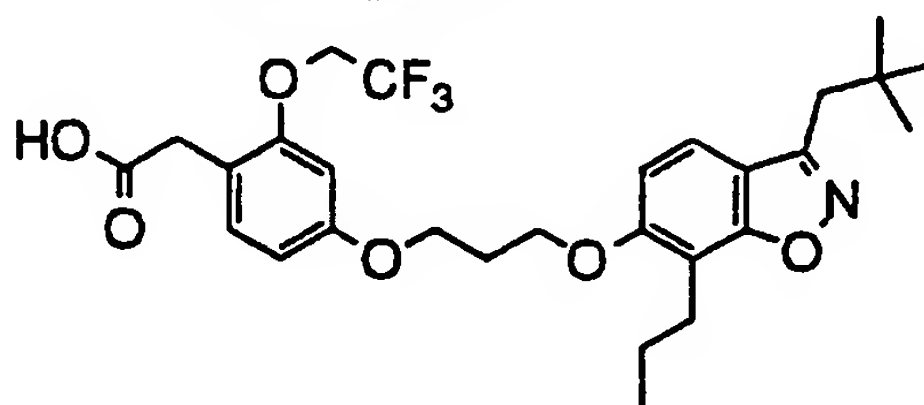
Using the method of Example 20, step D, methyl 2,3-dichloro-4-(3-(3-neo-pental-7-propyl-6-benz-[4,5]-isoxazoloxy)propylthio)-phenylacetate as the starting material, the title compound was obtained.

- 128 -

^1H NMR(300MHz, CDCl_3): δ 7.36 (d, 1H, $J = 8.7$ Hz), 7.17 (d, 1H, $J = 8.3$ Hz), 7.13 (d, 1H, $J = 8.2$ Hz), 6.89 (d, 1H, $J = 8.7$ Hz), 4.19 (t, 2H, $J = 5.8$ Hz), 3.76 (s, 2H), 3.19 (t, 2H, $J = 7.2$ Hz), 2.88 (t, 2H, $J = 7.5$ Hz), 2.81 (s, 2H), 2.22 (quint, 2H, $J = 7.1$ Hz), 1.71 (hex, 2H, $J = 7.3$ Hz), 1.05 (s, 9H), 0.96 (t, 3H, $J = 7.3$ Hz)

ESI: MS $m/e = 524$ ($M+1$)

Example 55



2-Trifluoroethoxy-4-(3-(3-neo-pental-7-propyl-6-benz-[4,5]-isoxazoloxy)propyloxy)phenylacetic acid

Step A: Preparation of methyl 2-trifluoroethoxy-4-(3-(3-neo-pental-7-propyl-6-benz-[4,5]-isoxazoloxy)propyloxy)phenylacetate

Using the method of Example 20, step C, 1-bromo-3-(3-neo-pental-7-propyl-6-benz-[4,5]-isoxazoloxy)phenoxypropane and methyl 2-trifluoroethoxy-4-hydroxyphenylacetate as the starting material, the title compound was obtained.

^1H NMR(300MHz, CDCl_3): δ 7.34 (d, 1H, $J = 8.7$ Hz), 7.08 (d, 1H, $J = 8.3$ Hz), 6.92 (d, 1H, $J = 8.7$ Hz), 6.52 (d, 1H, $J = 2.4$ Hz), 6.42 (dd, 1H, $J = 8.4, 2.5$ Hz), 4.30 (2H, $J = 8.2$ Hz), 4.21 (t, 2H, $J = 6.1$ Hz), 4.16 (t, 2H, $J = 5.9$ Hz), 3.55 (s, 3H), 3.53 (s, 2H), 2.83 (t, 2H, $J = 7.5$ Hz), 2.78 (s, 2H), 2.27 (quint, 2H, $J = 6.5$ Hz), 1.65 (hex, 2H, $J = 7.5$ Hz), 1.02 (s, 9H), 0.92 (t, 3H, $J = 7.3$ Hz)

Step B: Preparation of 2-trifluoroethoxy-4-(3-(3-neo-pental-7-propyl-6-benz-[4,5]-isoxazoloxy)propyloxy)phenylacetic acid

Using the method of Example 20, step D, methyl 2-trifluoroethoxy-4-(3-(3-neo-pental-7-propyl-6-benz-[4,5]-isoxazoloxy)-

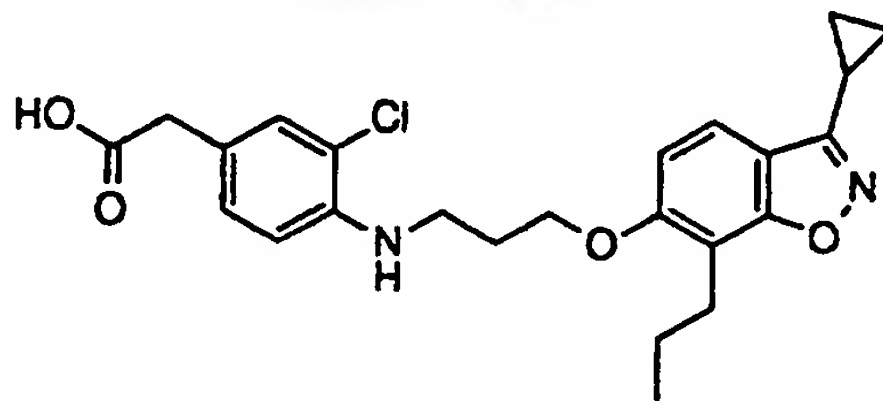
- 129 -

propylthio)phenylacetate as the starting material, the title compound was obtained.

^1H NMR(300MHz, CDCl_3): δ 7.34 (d, 1H, $J = 8.7$ Hz), 7.08 (d, 1H, $J = 8.3$ Hz), 6.92 (d, 1H, $J = 8.7$ Hz), 6.52 (d, 1H, $J = 2.4$ Hz), 6.42 (dd, 1H, $J = 8.4, 2.5$ Hz), 4.30 (2H, $J = 8.2$ Hz), 4.21 (t, 2H, $J = 6.1$ Hz), 4.16 (t, 2H, $J = 5.9$ Hz), 3.53 (s, 2H), 2.83 (t, 2H, $J = 7.5$ Hz), 2.78 (s, 2H), 2.27 (quint, 2H, $J = 6.5$ Hz), 1.65 (hex, 2H, $J = 7.5$ Hz), 1.02 (s, 9H), 0.92 (t, 3H, $J = 7.3$ Hz)

ESI: MS $m/e = 538$ (M+1)

Example 56



3-Chloro-4-(3-(3-cyclopropyl)-7-propyl-6-benz-[4,5]-isoxazoloxy)propylamino)phenylacetate

Step A: Preparation of 4-cyclopropylcarbonyl-2-(n-propyl)resorcinol

Using the method of Example 50, Step B, substituting cyclopropylcarboxylic acid as the starting material, the title compound was obtained as a coral-colored solid. NMR (CDCl_3); δ 1.00 (t, 3H); 1.05 (m, 2H); 1.27 (m, 2H); 1.60 (m, 2H); 2.62 (m, 1H); 2.65 (t, 2H); 6.40 (d, 1H); 7.76 (d, 1H).

Step B: Preparation of 4-cyclopropylhydroxyimino-2-(n-propyl)resorcinol

A solution of 4-cyclopropylcarbonyl-2-(n-propyl)resorcinol (1.0 g, 4.54 mmole) in methanol (10 mL) was treated with hydroxylamine-HCl (1.58g, 22.7 mmole) and sodium acetate (1.86g, 22.7 mmole) and the mixture refluxed for 7 hours. The cooled mixture was poured into water and extracted 3x with ethyl acetate. The

- 130 -

combined extracts were washed with water (2x), 10% sodium bicarbonate, brine, dried over magnesium sulfate and concentrated *in vacuo* to give a solid. The crude product was chromatographed on silica gel eluting with methylene chloride followed by methanol:methylene chloride (5:95) to afford the title compound. NMR (CDCl₃); δ 0.89 (m, 2H); 0.94 (t, 3H); 1.10 (m, 2H); 1.76 (m, 1H); 2.61 (t, 2H); 6.35 (d, 1H); 7.41 (d, 1H).

Step C: Preparation of 3-cyclopropyl-6-hydroxy-7-propylbenz-[4,5]-isoxazole

A solution of 4-cyclopropylhydroxyimino-2-(n-propyl)resorcinol (537 mg, 2.28 mmole) in acetic anhydride (6 mL) was stirred at room temperature for 2 days. The mixture was concentrated *in vacuo* and the residue partitioned with ethyl acetate and 10% sodium carbonate and stirred for 1 hour. The organic phase was washed with brine, dried over magnesium sulfate and concentrated *in vacuo* to give a solid. Flash chromatography on silica gel in ethyl acetate:hexane (15:85) afforded the title compound (150 mg) as a solid. NMR (CDCl₃); δ 1.00 (t, 3H); 1.17 (m, 2H); 1.26 (m, 2H); 1.74 (m, 2H); 2.25 (m, 1H); 2.82 (t, 2H); 6.77 (d, 1H); 7.27 (d, 1H).

Step D: Preparation of methyl 3-chloro-4-(3-(3-cyclopropyl)-7-propyl-6-benz-[4,5]-isoxazoloxy)propylamino)phenylacetate

To a solution of 3-cyclopropyl-6-hydroxy-7-propylbenz-[4,5]-isoxazole (34 mg, 0.156 mmole) and methyl 3-chloro-4-(3-bromopropylamino)phenylacetate (Example 21, Step C, 50 mg, 0.156 mmole) in DMF (0.70 mL) was added cesium carbonate (54 mg, 0.164 mmole), and the mixture stirred at 80°C in a nitrogen atmosphere for 2 hours. The cooled mixture was dissolved in ethyl acetate and washed with water, brine, dried over magnesium sulfate and concentrated *in vacuo* to give an oil. Thin layer chromatography on silica gel eluting with hexane:ethyl acetate (2:1) afforded the title compound (44 mg). NMR (CDCl₃); δ 0.95 (t, 3H); 1.15 (m, 2H); 1.24 (m, 2H); 1.67 (m, 2H); 2.15 (t, 2H); 2.18 (m, 1H); 2.81 (t, 2H); 3.43 (t, 2H); 3.47 (s, 2H);

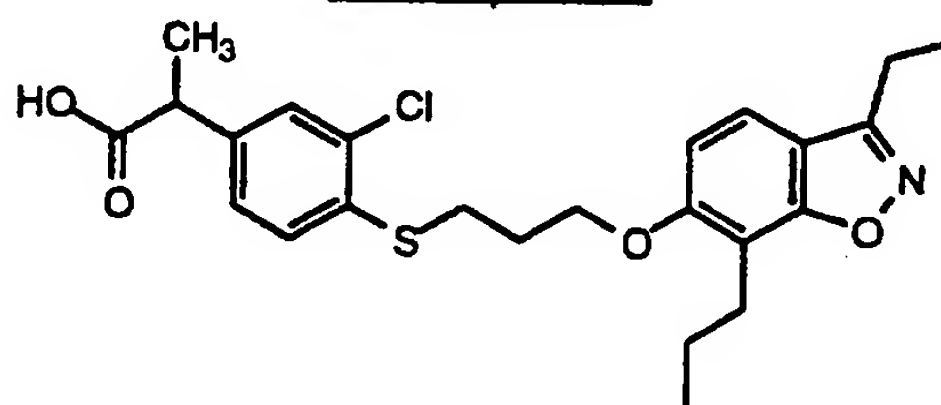
- 131 -

3.67 (s, 3H); 4.10 (t, 2H); 6.65 (d, 1H); 6.83 (d, 1H); 7.04 (d, 1H); 7.18 (d, 1H); 7.32 (d, 1H).

Step E: Preparation of 3-chloro-4-(3-(3-cyclopropyl)-7-propyl-6-benz-[4,5]-isoxazoloxy)propylamino)phenylacetate

Using the method of Example 22, substituting methyl 3-chloro-4-(3-(3-cyclopropyl)-7-propyl-6-benz-[4,5]-isoxazoloxy)propylamino)phenylacetate as starting material, the title compound was obtained. NMR (CD₃OD); δ 0.95 (t, 3H); 1.3 (m, 4H); 1.69 (m, 2H); 2.13 (m, 2H); 2.2 (m, 1H); 2.85 (t, 2H); 3.42 (t, 2H); 3.43 (s, 2H); 4.13 (m, 2H); 6.72 (d, 1H); 6.98 (d, 1H); 7.03 (dd, 1H); 7.17 (d, 1H); 7.29 (d, 1H).

Example 57



2-(3-chloro-4-(3-(3-ethyl-7-propyl-6-benz-[4,5]-isoxazoloxy)propylthio)) phenylpropionic acid

1. 3-ethyl-6-(3-bromopropyl)oxy-7-propylbenz[4,5]isoxazole

A solution of 3-ethyl-6-hydroxy-7-propylbenz[4,5]isoxazole (2.00 grams; 9.74 mmol) in dry DMF was treated with dibromopropane (7.17 mL; 38.97 mmol) and cesium carbonate (3.49 grams; 10.71 mmol). The solution was stirred at room temperature for 10 hours, then partitioned between isopropyl acetate and pH 4.0 buffer. The organic layer was washed twice with water, dried over magnesium sulfate, filtered and concentrated *in vacuo*. Silica gel chromatography afforded the title compound (1.74 g).

NMR (CDCl₃): 7.39 (d, 1H, J = 8.8 Hz); 6.91 (d, 1H, J = 8.8 Hz); 4.18 (t, 2H, J = 5.7 Hz); 3.63 (t, 2H, J = 6.4 Hz); 2.94 (quart, 2H, J = 7.6 Hz); 2.35 (quint, 2H, J = 6.0 Hz); 1.40 (t, 3H, J = 7.5 Hz); 0.94 (t, 3H, 7.4 Hz).

- 132 -

2. 2-(3-chloro-4-(3-(3-ethyl-7-propyl-6-benz[4,5]isoxazole)oxy)propylthio) phenyl propionic acid methyl ester

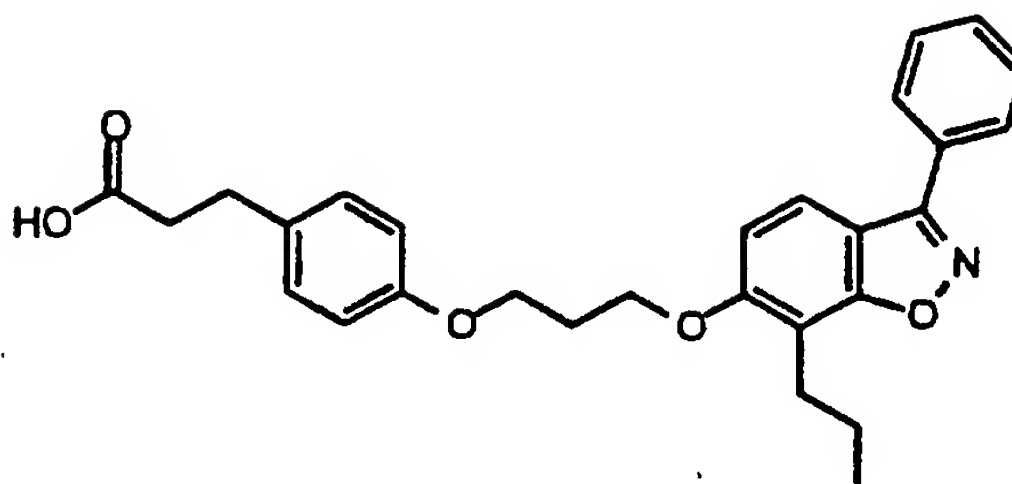
A solution of 2-(3-chloro-4-dimethylcarbamoylthio)phenyl propionic acid methyl ester (0.106 g; 0.352 mmol) in dry methanol (1.42 mL) was treated with a solution of sodium methoxide in methanol (4.37 M; 0.113 mL; 0.493 mmol). The solution was refluxed for 4 hours and then cooled to room temperature. 3-ethyl-6-(3-bromopropyl)oxy-7-propyl-benz[4,5]isoxazole (0.096 grams; 0.293 mmol) was added and the reaction stirred for 1 hour. The reaction mixture was partitioned between isopropyl acetate and pH 4.0 buffer. The organic layer was dried over magnesium sulfate, filtered and evaporated. Silica gel chromatography afforded the title compound. NMR (CDCl₃): 7.38 (d, 1H, J = 8.4 Hz); 7.25 (d, 1H, J = 5.4 Hz); 7.15 (d, 1H, J = 8.1 Hz); 6.87 (d, 1H, J = 8.7); 4.17 (t, 2H, J = 5.6 Hz); 3.66 (quart, 1H, J = 7.0 Hz); 3.60 (s, 3H); 3.15 (t, 2H, J = 7.0 Hz); 2.94 (quart, 2H, J = 7.6 Hz); 2.85 (t, 2H, J = 7.5); 1.66 (quart, 2H, J = 7.1 Hz); 1.40 (t, 2H, J = 7.5 Hz).

3. 2-(3-chloro-4-(3-(3-ethyl-7-propyl-6-benz[4,5]isoxazole)oxy)propylthio) phenyl propionic acid

A solution of 2-(3-chloro-4-(3-(3-ethyl-7-propyl-6-benz[4,5]isoxazole)oxy)propylthio)phenyl propionic acid methyl ester (0.037 g; 0.076 mmol) in ethanol (1.0 mL) was treated with a solution of potassium hydroxide in water (1.0M; 0.153 mL; 0.153 mmol). The solution was refluxed for 1 hour. The reaction mixture was partitioned between isopropyl acetate and 0.1 N HCl. The organic was dried over magnesium sulfate, filtered and concentrated to afford the title compound.

NMR (CDCl₃): 7.38 (d, 1H, J = 8.4 Hz); 7.25 (d, 1H, J = 5.4 Hz); 7.15 (d, 1H, J = 8.1 Hz); 6.87 (d, 1H, J = 8.7); 4.17 (t, 2H, J = 5.6 Hz); 3.66 (quart, 1H, J = 7.0 Hz); 3.15 (t, 2H, J = 7.0 Hz); 2.94 (quart, 2H, J = 7.6 Hz); 2.85 (t, 2H, J = 7.5); 1.66 (quart, 2H, J = 7.1 Hz); 1.40 (t, 2H, J = 7.5 Hz).

- 133 -

Example 58

3-(4-(3-(3-phenyl-7-propyl-6-benz-[4,5]-isoxazoloxy)propyloxy))
phenylpropionic acid

Step 1

The methyl 3-(4-(3-bromoprop-1-oxy)phenyl)propionate can be obtained from commercially available methyl 3-(4-hydroxyphenyl)propionate and 1,3-dibromopropane as described in Example 16 Step 4. The product was purified by elution from a silica gel column (E. Merck 40-63 μ) with hexanes : methylene chloride 50 : 50.

Characteristic NMR Resonances; ^1H NMR 400MHz (CDCl_3); 6.95 (ABq, 4H), 4.06 (t, 2H, $J = 5.8$ Hz), 3.65 (s, 3H), 3.58 (t, 2H, $J = 6.4$ Hz), 2.87 (t, 2H, $J = 8.0$ Hz), 2.58 (t, 2H, $J = 6.5$ Hz), 2.28 (pent, 2H, $J = 5.9$ Hz).

Step 2

The 3-phenyl-6-hydroxy-7-propylbenzisoxazole of Example 16 Step 3 (37 mg, 1.0 Eq, 0.145 mmol) was coupled with the bromide of Example 59 Step 1 (49 mg, 1.1 Eq, 0.16 mmol) as described in the procedure of Example 16 Step 4. The product was purified by elution from a silica gel column (2.5 g E. Merck 40-63 μ) with toluene : hexanes : EtOAc 60 : 35 : 5.

Characteristic NMR Resonances; ^1H NMR 400MHz (CDCl_3); 7.92 (m, 2H), 7.64 (d, 1H, $J = 8.7$ Hz), 7.5-7.3 (m, 2H), 7.09 (d, 1H, $J = 8.8$ Hz), 6.99 (d, 1H, $J = 8.8$ Hz), 6.83 (m, 2H), 4.26 (t, 2H, $J = 6.1$ Hz), 4.17 (t,

- 134 -

2H, $J = 6.1$ Hz), 2.90 (m, 4H), 2.57 (t, 2H, $J = 8.1$ Hz), 2.30 (pent, 2H, $J = 6.1$ Hz), 1.69 (sext, 2H, $J = 7.5$ Hz), 0.946 (t, 3H, $J = 7.3$ Hz).
MS ESI $M+1 = 474.3$. MW = 473.2

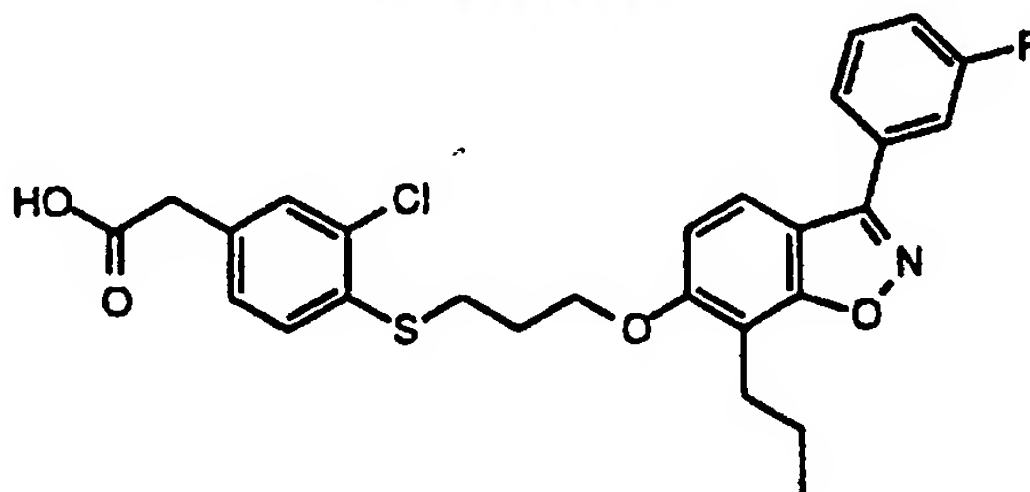
Step 3

The ester of Example 58 Step 2 (46 mg, 1.0 Eq, 0.096 mmol) was hydrolyzed with LiOH (150 μ L, 1.5 N, 2.3 Eq, 0.255 mmol) as described in Example 16 Step 5.

Characteristic NMR Resonances; ^1H NMR 400MHz (CDCl_3); 7.9-7.93 (m, 2H), 7.64 (d, 1H, $J = 8.7$ Hz), 7.5-7.55 (m, 3H), 7.10 (d, 1H, $J = 8.7$ Hz), 6.99 (d, 1H, $J = 8.7$ Hz), 6.83 (d, 1H, $J = 8.7$ Hz), 4.26 (t, 2H, $J = 5.98$ Hz), 4.17 (t, 2H, $J = 6.03$ Hz), 2.88 (t, 2H, $J = 8.4$ Hz), 2.90 (t, 2H, $J = 7.7$ Hz), 2.62 (t, 2H, $J = 8.1$ Hz), 2.30 (pent, 2H, $J = 6.1$ Hz), 1.69 (sext, 2H, $J = 7.5$ Hz), 0.945 (t, 3H, $J = 7.4$ Hz).

Analytical HPLC 75 : 25 $\text{CH}_3\text{CN} : \text{H}_2\text{O}$ 0.1 % TFA, E. Merck RP-8 5μ 4 X 250 mm, 1 ml/min. UV 210, RT 6.47 min.

MS ESI $M+1 = 460.3$. MW = 459.2

Example 59

3-Chloro-4-(3-(3-(3-fluorophenyl)-7-propyl-6-benz-[4,5]-isoxazoloxy)-propylthio)phenylacetic acid

Step 1

Commercially available 2-propylresorcinol (3.0 g, 1.0 Eq, 0.02 mol) and meta-fluorobenzoic acid (3.2 g, 1.15 Eq, 0.023 mol) were condensed as described in Example 51 Step 1.

The product was purified by elution from a silica gel column (20 g E. Merck 40-63 μ) with toluene : hexanes : EtOAc 60 : 35 : 5.

- 135 -

Characteristic NMR Resonances; ^1H NMR 400MHz (CDCl_3); 7.42-7.47 (m, 1H), 7.36-7.4 (m, 1H), 7.29-7.33 (m, 1H), 7.2-7.26 (m, 1H), 6.31 (d, 1H, $J = 8.8$ Hz), 2.66 (dd, 2H, $J = 9.3, 7.6$ Hz), 1.61 (sext, 2H, $J = 7.7$ Hz), 0.994 (t, 3H, $J = 7.4$ Hz).

MS ESI $M+1 = 275.1$. MW = 274.1

Step 2

The ketone of Example 59 Step 1 (2.6 g, 1.0 Eq, 9.4 mmol) was converted to the oxime with $\text{NH}_2\text{OH}\cdot\text{HCl}$ (0.7 g, 1.05 Eq, 9.8 mmol) as described in the procedure of Example 7 Step A. Heating was continued for 72 Hrs. The product was purified by elution from a silica gel column (112 g E. Merck 40-63 μ) with toluene : EtOAc 97 : 3.

Characteristic NMR Resonances; ^1H NMR 400MHz (CDCl_3); 7.0 - 7.5 (four 1H multiplets), 6.49 (d, 1H, $J = 8.7$ Hz), 6.21 (d, 1H, $J = 8.8$ Hz), 2.66 (dd, 2H, $J = 9.3, 7.6$ Hz), 1.61 (sext, 2H, $J = 7.7$ Hz), 0.996 (t, 3H, $J = 7.4$ Hz).

Step 3

The oxime of Example 59 step 2 (846 mg, 2.9 mmol) was converted to the 3-(meta-fluorophenyl)-6-hydroxy-7-propylbenzisoxazole as described in Example 7 Step A. The product was purified by recrystallization from toluene.

Characteristic NMR Resonances; ^1H NMR 400MHz (CDCl_3); 7.69 (m, 1H), 7.61 (m, 1H), 7.55 (d, 1H, $J = 8.5$ Hz), 7.50 (m, 1H), 7.20 (m, 1H), 6.88 (d, 1H, $J = 8.5$ Hz), 5.23 (s, 1H), 2.91 (t, 2H, $J = 7.5$ Hz), 1.75 (sext, 2H, $J = 7.5$ Hz), 1.01 (t, 3H, $J = 7.3$ Hz).

MS ESI $M+1 = 272.1$. MW = 271.1

Step 4

The 3-(meta-fluorophenyl)-6-hydroxy-7-propylbenzisoxazole of Example 59 Step 3 (34 mg, 1.0 Eq, 0.123 mmol) was coupled with the bromide of Example 16 Step 1A (43 mg, 1.05 Eq, 0.128 mmol) as described in Example 16 Step 4. The product was

- 136 -

purified by elution from a silica gel column (3 g E. Merck 40-63 μ) with toluene : hexanes : EtOAc 60 : 35 : 5.

Characteristic NMR Resonances; ^1H NMR 400MHz (CDCl_3); 7.72 (m, 1H), 7.6 (m, 1H), 7.63 (d, 1H, $J = 8.8$ Hz), 7.51 (dt, 1H), 7.31 (d, 1H, $J = \sim 1.5$ Hz), 7.27 (d, 1H, $J = 8.1$ Hz), 7.21 (dt, 1H), 7.12 (dd, 1H), 6.97 (d, 1H, $J = 8.8$ Hz), 4.21 (t, 2H, $J = 5.8$ Hz), 3.68 (s, 3H), 3.55 (s, 2H), 3.17 (t, 2H, $J = 7$ Hz), 2.92 (dd, 2H, J unresolved), 2.19 (pent, 2H), 1.71 (sext, 2H, $J = 7.5$ Hz), 0.964 (t, 3H, $J = 7.4$ Hz).

MS ESI $M+1 = 528.2$. MW = 527.1

Step 5

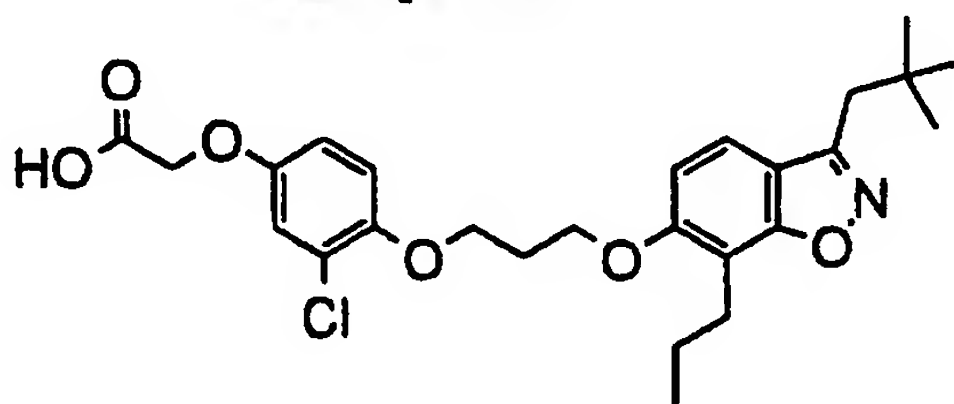
The ester of Example 59 Step 4 (51 mg, 1.0 Eq, 0.097 mmol) was hydrolyzed with LiOH (150 μL , 1.5 N, 2.3 Eq, 0.225 mmol) as described in Example 16 Step 5. The product was purified by elution from a reversed phase RP-8 col (10 g E. Merck 40-63 μ) with 75 : 25 $\text{CH}_3\text{CN} : \text{H}_2\text{O}$ 0.1 % TFA.

Characteristic NMR Resonances; ^1H NMR 400MHz (CDCl_3); 7.70 (dd, 1H), 7.62 (d, 1H, $J = 8.7$ Hz), 7.62 (m, 1H), 7.50 (dt, 1H), 7.31 (d, 1H, $J = 1.9$ Hz), 7.28 (d, 1H, $J = 8.1$ Hz), 7.20 (dt, 1H), 7.12 (dd, 1H), 6.97 (d, 1H, $J = 8.8$ Hz), 4.21 (t, 2H, $J = 5.8$ Hz), 3.69 (s, 2H), 3.18 (t, 2H, $J = 7.1$ Hz), 2.91 (dd, 2H, $J = 8.8, 7.5$ Hz), 2.19 (pent, 2H), 1.71 (sext, 2H, $J = 7.7$ Hz), 0.96 (t, 3H, $J = 7.4$ Hz).

Analytical HPLC 75 : 25 $\text{CH}_3\text{CN} : \text{H}_2\text{O}$ 0.1 % TFA, E. Merck RP-8 5 μ 4 X 250 mm, 1 ml/min. UV 210, RT 7.55 min.

MS ESI $M+1 = 514.3$. MW = 513.1

Example 60



3-Chloro-4-(3-(3-neo-pental-7-propyl-6-benz-[4,5]-isoxazoloxy)-propyloxy)phenoxyacetic acid

- 137 -

Step A: Preparation of methyl 3-chloro-4-hydroxyphenoxylacetate

A solution of chlorohydroxyquinone (5.0 g), ethyl bromoacetate (3.84 mL) and potassium carbonate (4.78 g) was refluxed for five hours. The mixture of reaction was partitioned between water and ether. The combined organics were washed with water and brine, dried over magnesium sulfate, poured onto a column of silica gel and eluted with ethyl acetate/hexane (20/80) to give the title compound.

¹H NMR(400MHz, CDCl₃): δ 6.92 (m, 2H), 6.77 (dd, 1H, J = 8.8, 3.0 Hz), 5.21 (s, 2H), 4.52 (s, 3H), 4.24 (quart, 2H, J = 7.2 Hz), 1.27 (t, 3H, J = 7.2 Hz).

Step B: Preparation of methyl 2-trifluoroethoxy-4-(3-(3-neo-pental-7-propyl-6-benz-[4,5]-isoxazoloxy)propyloxy)phenylacetate

Using the method of Example 20, step C, 1-bromo-3-(3-neo-pental-7-propyl-6-benz-[4,5]-isoxazoloxy)phenoxypropane and methyl 2-trifluoroethoxy-4-hydroxyphenylacetate as the starting material, the title compound was obtained.

¹H NMR(400MHz, CDCl₃): δ 7.34 (d, 1H, J = 8.7 Hz), 6.97 (d, 1H, J = 3.0 Hz), 6.93 (d, 1H, J = 8.7 Hz), 6.87 (d, 1H, J = 9.0 Hz), 6.77 (dd, 1H, J = 9.0, 3.0 Hz), 4.52 (s, 2H), 4.27 (s, 4H), 4.16 (t, 2H, J = 5.9 Hz), 2.82 (t, 2H, J = 7.4 Hz), 2.78 (s, 2H), 2.31 (quint, 2H, J = 6.0 Hz), 1.65 (hex, 2H, J = 7.3 Hz), 1.26 (t, 2H, J = 7.1 Hz), 1.02 (s, 9H), 0.90 (t, 3H, J = 7.3 Hz)

Step C: Preparation of 2-trifluoroethoxy-4-(3-(3-neo-pental-7-propyl-6-benz-[4,5]-isoxazoloxy)propyloxy)phenylacetic acid

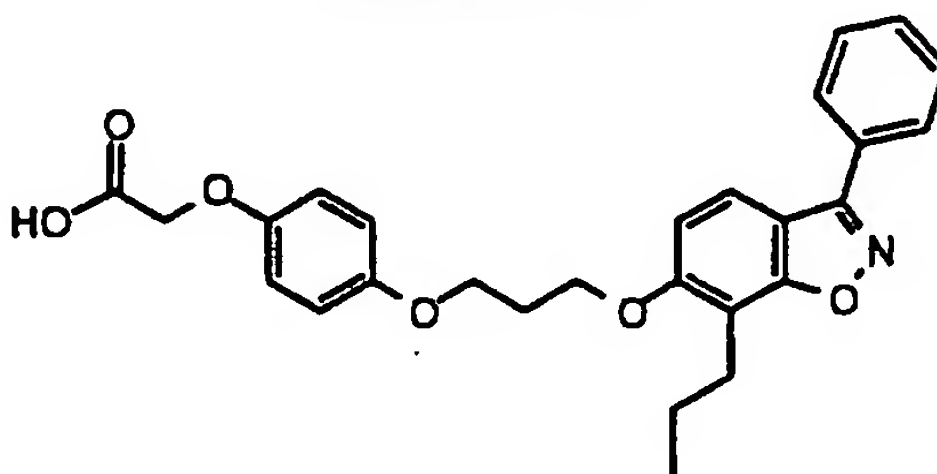
Using the method of Example 20, step D, methyl 2-trifluoroethoxy-4-(3-(3-neo-pental-7-propyl-6-benz-[4,5]-isoxazoloxy)propylthio)phenylacetate as the starting material, the title compound was obtained.

¹H NMR(400MHz, CDCl₃): δ 7.34 (d, 1H, J = 8.7 Hz), 6.97 (d, 1H, J = 3.0 Hz), 6.93 (d, 1H, J = 8.7 Hz), 6.87 (d, 1H, J = 9.0 Hz), 6.77 (dd, 1H, J = 9.0, 3.0 Hz), 4.60 (s, 2H), 4.27 (t, 2H, J = 5.9 Hz), 4.18 (t, 2H, J =

- 138 -

5.9 Hz), 2.82 (t, 2H, J = 7.4 Hz), 2.78 (s, 2H), 2.31 (quint, 2H, J = 6.0 Hz), 1.65 (hex, 2H, J = 7.3 Hz), 1.02 (s, 9H), 0.90 (t, 3H, J = 7.3 Hz)
ESI: MS m/e = 490 (M+1)

Example 61



4-(3-(3-phenyl-7-propyl-6-benz[4,5]isoxazole)oxy)propyloxy phenoxy acetic acid

Step 1

The 6-(3-bromoprop-1-oxy)-3-phenyl-7-propylbenzisoxazole can be prepared as in Example 1 Step A from 6-hydroxy-3-phenyl-7-propylbenzisoxazole (1.5 g, 1.0 Eq, 6 mmol), prepared as described in Example 16 Step 3, and 1,3-dibromopropane (3.0 ml, 5 Eq, 30 mmol).

The product was purified by elution from a silica gel column (100 g E. Merck 40-63 μ) with toluene : hexanes : EtOAc 30 : 65 : 5.

Characteristic NMR Resonances; ^1H NMR 400MHz (CDCl_3); 7.91 (m, 2H), 7.65 (d, 1H, J = 8.7 Hz), 7.5-7.55 (m, 3H), 7.24 (m, 1H), 7.16 (m, 1H), 7.69 (d, 1H, J = 8.7 Hz), 4.22 (t, 2H, J = 5.7 Hz), 3.65 (t, 2H, J = 6.4 Hz), 2.9 (t, 2H, J = 7.4 Hz), 2.38 (pent, 2H, J = 5.9 Hz), 1.71 (sext, 2H, J = 7.4 Hz), 0.977 (t, 3H, J = 7.4 Hz).

MS ESI M+1 = 360.0 / 362. MW = 359.1 / 361.1 (Bromine isotopes).

Step 2

Commercially available 4-hydroxyphenoxyacetic acid (2 g) was esterified as described in Example 23 Step 1. The ester was used without purification further.

- 139 -

Characteristic NMR Resonances; ^1H NMR 400MHz (CDCl_3); 6.76 (Aromatic ABq, 4H), 4.56 (s, 2H), 3.78 (s, 3H).

MS CI NH_3 $\text{M}+\text{NH}_4^+ = 200$. MW = 182.1

Step 3

The 6-(3-bromoprop-1-oxy)-3-phenyl-7-propylbenzisoxazole of Example 62 Step 1 (56.4 mg, 1.0 Eq, 0.15 mmol) was coupled with the methyl 4-hydroxyphenoxyacetate of Example 61 Step 2 (32 mg, 1.15 Eq, 0.176 mmol) as described in the procedure of Example 16 Step 4.

The product was purified by elution from a silica gel column (4 g E. Merck 40-63 μ) with toluene : hexanes : EtOAc 60 : 35 : 5.

Characteristic NMR Resonances; ^1H NMR 400MHz (CDCl_3); 7.91 (m, 2H), 7.64 (d, 1H, $J = 8.8$ Hz), 7.52 (m, 3H), 6.99 (d, 1H, $J = 8.8$ Hz), 6.84 (s, 4H), 4.57 (s, 2H), 4.26 (t, 2H, $J = 5.9$ Hz), 4.14 (t, 2H, $J = 6.1$ Hz), 3.78 (s, 3H), 2.90 (dd, 2H, J unresolved), 2.29 (pent, 2H, $J = 6.1$ Hz), 1.70 (sext, 2H), 0.946 (t, 3H, $J = 7.4$ Hz).

MS ESI $\text{M}+1 = 476.2$. MW = 475.2.

Step 4

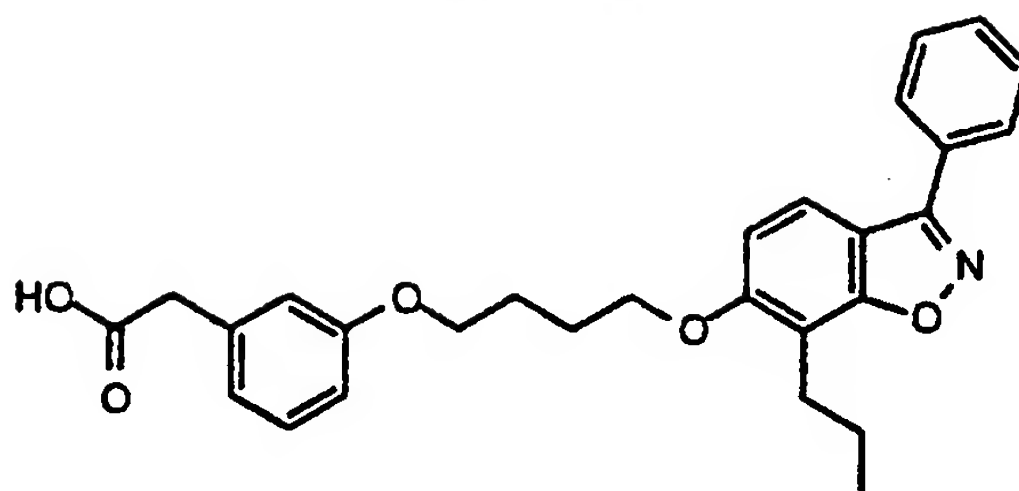
The ester of Example 61 Step 3 (44 mg, 1.0 Eq, 0.092 mmol) was hydrolyzed with LiOH (130 μL , 1.5 N, 2 Eq, 0.195 mmol) as described in Example 16 Step 5.

Characteristic NMR Resonances; ^1H NMR 400MHz (CDCl_3); 7.92 (m, 2H), 7.66 (d, 1H, $J = 8.7$ Hz), 7.52 (m, 3H), 6.99 (d, 1H, $J = 8.8$ Hz), 6.87 (s, 4H), 4.62 (s, 2H), 4.28 (t, 2H, $J = 5.9$ Hz), 4.17 (t, 2H, $J = 6.0$ Hz), 2.92 (dd, 2H, J unresolved), 2.31 (pent, 2H, $J = 6.1$ Hz), 1.71 (sext, 2H, $J = 7.5$ Hz), 0.964 (t, 3H, $J = 7.3$ Hz).

Analytical HPLC 75 : 25 CH_3CN : H_2O 0.1 % TFA, E. Merck RP-8 5 μ 4 X 250 mm, 1 ml/min. UV 210, RT 5.47 min.

MS ESI $\text{M}+1 = 462.3$. MW = 461.2

- 140 -

Example 62

(3-(4-(3-phenyl-7-propyl-6-benz-[4,5]-isoxazoloxy)butyloxy))
phenylacetic acid

Step 1

The 6-(4-bromobut-1-oxy)-3-phenyl-7-propylbenzisoxazole can be prepared as in Example 1 Step A from 6-hydroxy-3-phenyl-7-propylbenzisoxazole (2 g, 1.0 Eq, 7.9 mmol), prepared as described in Example 16 Step 3, and 1,4-dibromobutane (4.8 ml, 5 Eq, 39.5 mmol).

The product was purified by elution from a silica gel column (100 g E. Merck 40-63 μ) with toluene : hexanes : EtOAc 30 : 65 : 5.

Characteristic NMR Resonances; ^1H NMR 400MHz (CDCl_3); 7.92 (m, 2H), 7.64 (d, 1H, $J = 8.8$ Hz), 7.53 (m, 3H), 6.95 (d, 1H, $J = 8.8$ Hz), 4.11 (t, 2H, $J = 5.9$ Hz), 3.51 (t, 2H, $J = 6.4$ Hz), 2.91 (t, 2H, $J = 7.5$ Hz), 2.12 (complex m, 2H), 2.03 (complex m, 2H), 1.71 (sext, 2H, $J = 7.5$ Hz), 0.977 (t, 3H, $J = 7.4$ Hz).

MS ESI $M+1 = 388.2 / 390.2$. MW = 387.1 / 389.1 (Bromine Isotopes).

Step 2

The methyl 3-hydroxyphenylacetic acid from Example 23 Step 1 (26 mg, 1.05 Eq, 0.15 mmol) and the 6-(4-bromobut-1-oxy)-3-phenyl-7-propylbenzisoxazole from Example 62 Step 1 (42 mg, 1.0 Eq, 0.108 mmol) were condensed as described in Example 16 Step 4.

The product was purified by elution from a silica gel column (3 g E. Merck 40-63 μ) with toluene : hexanes : EtOAc 60 : 35 : 5.

- 141 -

Characteristic NMR Resonances; ^1H NMR 400MHz (CDCl_3); 7.92 (m, 2H), 7.64 (d, 1H, $J = 8.8$ Hz), 7.53 (m, 3H), 7.22 (t, 1H), 6.97 (d, 1H, $J = 8.8$ Hz), 6.83 (m, 3H), 4.14 (t, 2H), 4.04 (t, 2H), 3.67 (s, 3H), 3.58 (s, 2H), 2.92 (dd, 2H, J unresolved), 2.02 (m, 4H), 1.71 (sext, 2H, $J = 7.5$ Hz) 0.968 (t, 3H, $J = 7.4$ Hz).

MS ESI $M+1 = 474.4$. MW = 473.

Step 3

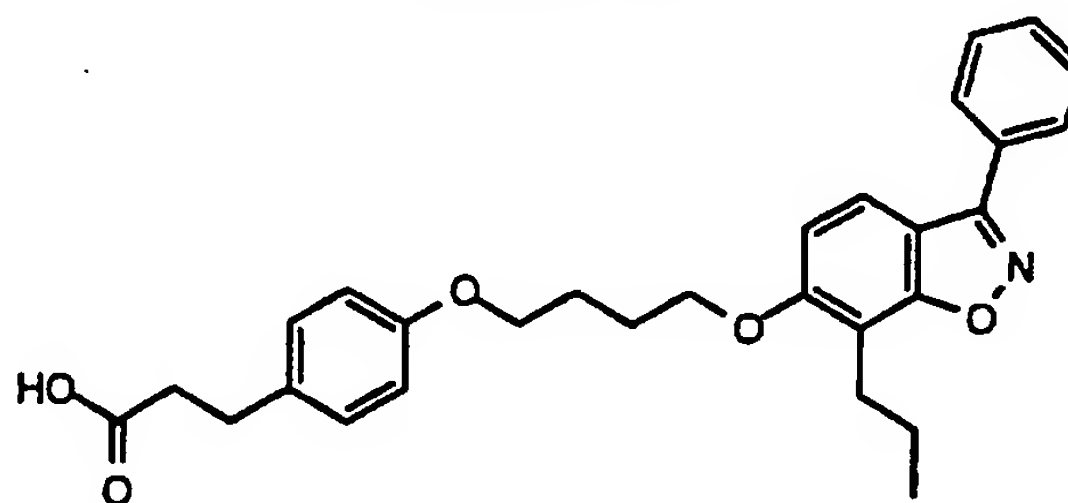
The ester of Example 62 Step 2 (46 mg, 1.0 Eq, 0.098 mmol) was hydrolyzed with LiOH (150 μL , 1.5 N, 2.3 Eq, 0.225 mmol) as described in Example 16 Step 5.

Characteristic NMR Resonances; ^1H NMR 400MHz (CDCl_3); 7.92 (m, 2H), 7.63 (d, 1H, $J = 8.8$ Hz), 7.52 (m, 3H), 7.22 (t, 1H), 6.96 (d, 1H, $J = 8.8$ Hz), 6.83 (m, 3H), 4.14 (t, 2H), 4.04 (t, 2H), 3.59 (s, 2H), 2.91 (dd, 2H, J unresolved), 2.02 (m, 4H), 1.71 (sext, 2H, $J = 7.5$ Hz), 0.963 (t, 3H, $J = 7.4$ Hz).

Analytical HPLC 75 : 25 CH_3CN : H_2O 0.1 % TFA, E. Merck RP-8 5μ 4 X 250 mm, 1 ml/min. UV 210, RT 6.61 min.

MS ESI $M+1 = 460.4$. MW = 459.2.

Example 63



3-(4-(4-(3-phenyl-7-propyl-6-benz-[4,5]-isoxazoloxy)butyloxy))phenylpropionic acid

Step 1

The 6-(4-bromobut-1-oxy)-3-phenyl-7-propylbenzisoxazole prepared in Example 62 Step 1 (48 mg, 1.0 Eq 0.124 mmol) and commercially available methyl 3-(4-hydroxyphenyl)propionate (26.3

- 142 -

mg, 1.15 Eq, 0.146 mmol) were condensed as described Example 16 Step 4.

The product was purified by elution from a silica gel column (2.5 g E. Merck 40-63 μ) with toluene : hexanes : EtOAc 60 : 35 : 5.

Characteristic NMR Resonances; ^1H NMR 400MHz (CDCl_3); 7.92 (m, 2H), 7.64 (d, 1H, $J = 8.8$ Hz), 7.52 (m, 3H), 7.09 (m, 2H), 6.97 (d, 1H, $J = 8.8$ Hz), 6.81 (m, 2H), 4.14 (t, 2H), 4.02 (t, 2H), 3.65 (s, 3H), 2.91 (t, 2H, $J = 7.5$ Hz), 2.89 (t, 2H, $J = 8.5$ Hz), 2.58 (t, 2H, $J = 7.5$ Hz), 2.01 (m, 4H), 1.71 (sext, 2H, $J = 7.5$ Hz), 0.964 (t, 3H, $J = 7.3$ Hz).

MS ESI $M+1 = 488.4$. MW = 487.2

Step 2

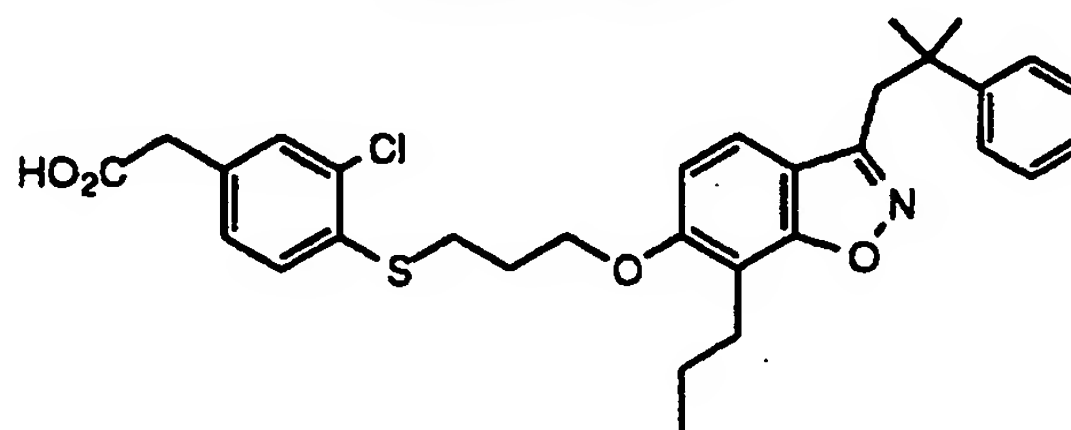
The ester of Example 63 Step 1 (49.3 mg, 1.0 Eq, 0.101 mmol) was hydrolyzed with LiOH (160 μL , 1.5 N, 2.3 Eq, 0.240 mmol) as described in Example 16 Step 5.

Characteristic NMR Resonances; ^1H NMR 400MHz (CDCl_3); 7.91 (m, 2H), 7.64 (d, 1H, $J = 8.8$ Hz), 7.52 (m, 3H), 7.10 (d, 2H, $J = 8.8$ Hz), 6.96 (d, 1H, $J = 8.8$ Hz), 6.81 (m, 2H), 4.14 (t, 2H), 4.02 (t, 2H), 2.89 (2 overlapping t, 4H), 2.65 (t, 2H, 8.1 Hz), 2.01 (m, 4H), 1.71 (sext, 2H), 0.964 (t, 3H, $J = 7.4$ Hz).

Analytical HPLC 75 : 25 $\text{CH}_3\text{CN} : \text{H}_2\text{O}$ 0.1 % TFA, E. Merck RP-8 5 μ 4 X 250 mm, 1 ml/min. UV 210, RT 7.22 min.

MS ESI $M+1 = 474.4$. MW = 473.2

EXAMPLE 64



3-chloro-4-(3-(2-methyl-2-phenylpropyl)-7-(n-propyl)-6-benz[4,5]isoxazoloxypentylthio)phenylacetic acid

- 143 -

Step A Preparation of 1,3-dihydroxy-4-(3-methyl-3-phenylbutyryl)-2-(n-propyl)benzene

Using the procedure in Example 51, step 1; 3-methyl-3-phenylbutyric acid and 2-(n-propyl)resorcinol were condensed in triflic acid to form 1,3-dihydroxy-4-(3-methyl-3-phenylbutyryl)-2-(n-propyl)benzene.

NMR (CDCl₃): d 7.14 - 7.41 (m, 6H); 6.24 (d, 1H); 5.30 (bs, 1H); 3.21 (s, 2H); 2.58 (t, 2H); 1.55 (m, 2H); 1.49 (s, 6H); 0.96 (t, 3H).

Step B Preparation of 3-(2-methyl-2-phenylpropyl)-6-hydroxy-7-(n-propyl)benz[4,5]isoxazole

Using the procedures in Example 51, steps 2 and 3, 1,3-dihydroxy-4-(3-methyl-3-phenylbutyryl)-2-(n-propyl)benzene was converted into 3-(2-methyl-2-phenylpropyl)-6-hydroxy-7-(n-propyl)benz[4,5]isoxazole.

NMR (CDCl₃): d 7.18 - 7.42 (m, 5H); 6.56 (d, 1H); 6.43 (d, 1H); 5.30 (vbs, 1H); 3.19 (s, 2H); 2.82 (t, 2H); 1.71 (m, 2H); 1.46 (s, 6H); 0.98 (t, 3H).

Step C Preparation of methyl 3-chloro-4-(3-(2-methyl-2-phenylpropyl)-7-(n-propyl)-6-benz[4,5]isoxazoloxy)propylthio)phenylacetate

Using the procedure Example 16, step 4, 3-(2-methyl-2-phenylpropyl)-6-hydroxy-7-(n-propyl)benz[4,5]isoxazole. and methyl 3-chloro-4-(3-bromopropylthio)phenylacetate were heated in DMF with Cs₂CO₃ to prepare methyl 3-chloro-4-(3-(2-methyl-2-phenylpropyl)-7-propyl-6-benz[4,5]isoxazoloxy)propylthio)phenylacetate.

NMR (CDCl₃): d 7.10 - 7.43 (m, 8H); 6.65 (d, 1H); 6.51 (d, 1H); 4.13 (t, 2H); 3.71 (s, 3H); 3.56 (s, 2H); 3.20 (s, 2H); 3.15 (t, 2H); 2.83 (t, 2H); 2.15 (m, 2H); 1.67 (m, 2H); 1.46 (s, 6H); 0.93 (t, 3H).

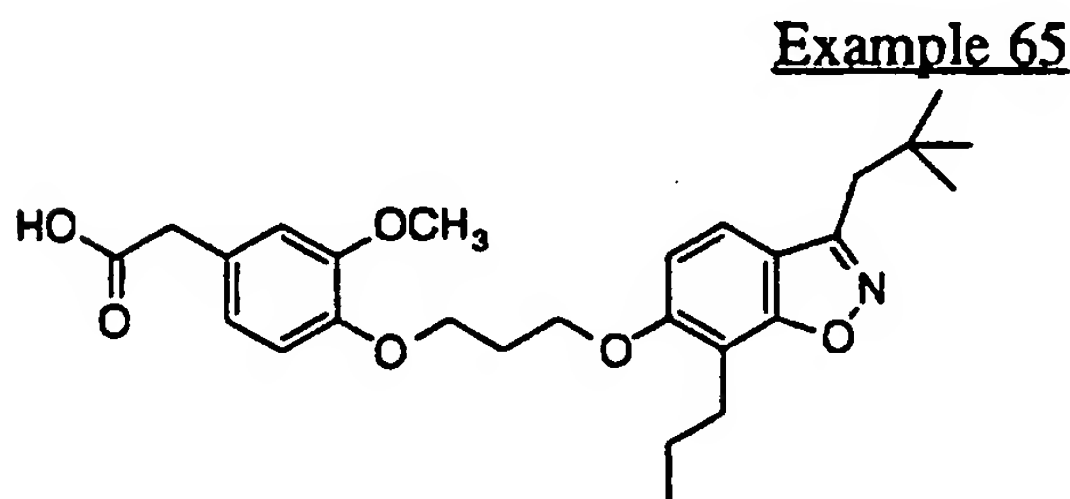
Step D Preparation of 3-chloro-4-(3-(2-methyl-2-phenylpropyl)-7-(n-propyl)-6-benz[4,5]isoxazoloxy)propylthio)phenylacetic acid

Using the procedure in Example 2, methyl 3-chloro-4-(3-(2-methyl-2-phenylpropyl)-7-(n-propyl)-6-

- 144 -

benz[4,5]isoxazoloxy)propylthio)-phenylacetate was saponified with LiOH to form 3-chloro-4-(3-(2-methyl-2-phenylpropyl)-7-propyl-6-benz[4,5]isoxazoloxy)propylthio)phenylacetic acid.

NMR (CDCl₃): δ 7.12 - 7.53 (m, 8H); 6.65 (d, 1H); 6.51 (d, 1H); 4.13 (t, 2H); 3.60 (s, 2H); 3.21 (s, 2H); 3.16 (t, 2H); 2.84 (t, 2H); 2.17 (m, 2H); 1.67 (m, 2H); 1.47 (s, 6H); 0.94 (t, 3H).



3-Methoxy-4-(3-(3-(2,2-dimethylpropyl)-7-propyl-6-benz-[4,5]-isoxazoloxy)propyloxy)phenylacetate

Step A: Preparation of 3-(2,2-dimethylpropyl)-6-(3-bromopropyloxy)-7-propyl-6-benz-[4,5]-isoxazole

To a solution of 3-(2,2-dimethylpropyl)-6-hydroxy-7-propyl-6-benz-[4,5]-isoxazole (1.00 g, 4.04 mmole) and 1,3-dibromopropane (2.05 mL, 20.2 mmole) in 2-butanone (20 mL) was added potassium carbonate (585 mg, 4.29 mmole) and the resulting mixture refluxed for 18 hours. The cooled mixture was filtered and the filtrate concentrated *in vacuo* to give an oil. Flash chromatography on silica gel eluting with methyl t-butyl ether:hexane (3:97) afforded the title compound (1.11g) as a white solid. NMR (CDCl₃); δ 0.99 (t, 3H); 1.07 (s, 9H); 1.72 (m, 2H); 2.39 (m, 2H); 2.83 (s, 2H); 2.90 (m, 2H); 3.67 (t, 2H); 4.22 (t, 2H); 6.94 (d, 1H); 7.39 (d, 1H).

Step B: Preparation of methyl 3-methoxy-4-(3-(3-(2,2-dimethylpropyl)-7-propyl-6-benz-[4,5]-isoxazoloxy)-propyloxy)-phenylacetate

Using the method of Example 56, Step D, and substituting 3-(2,2-dimethylpropyl)-6-(3-bromopropyloxy)-7-propyl-6-benz-[4,5]-isoxazole and methyl 4-hydroxy-3-methoxyphenylacetate as starting

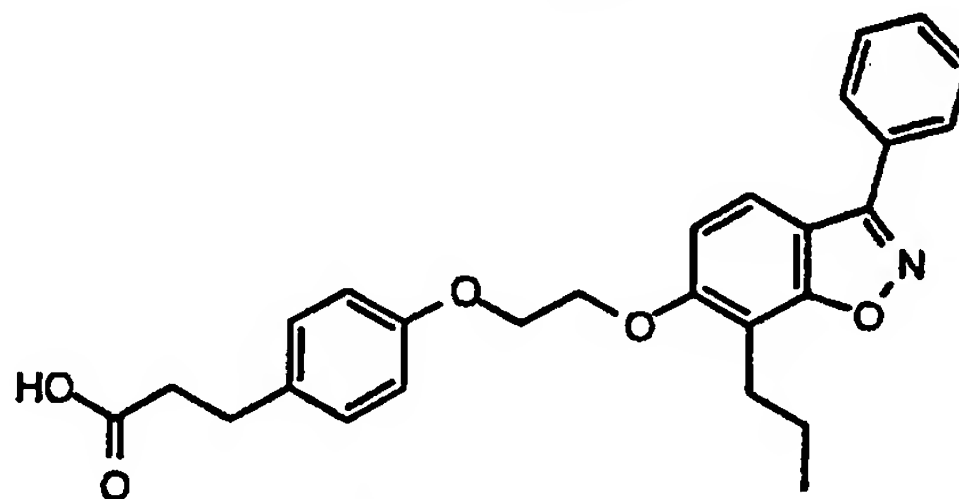
- 145 -

materials, the title compound was obtained as a gum. NMR (CDCl₃); δ 0.98 (t, 3H); 1.07 (s, 9H); 1.69 (m, 2H); 2.37 (m, 2H); 2.82 (s, 2H); 2.88 (t, 2H); 3.58 (s, 2H); 3.71 (s, 3H); 3.85 (s, 3H); 4.26 (m, 4H); 6.83 (m, 2H); 6.88 (d, 1H); 6.95 (d, 1H); 7.37 (d, 1H).

Preparation of 3-methoxy-4-(3-(3-(2,2-dimethylpropyl)-7-propyl-6-benz-[4,5]-isoxazoloxy)propyloxy)phenylacetate

Using the method of Example 37, Step E and substituting methyl 3-methoxy-4-(3-(3-(2,2-dimethylpropyl)-7-propyl-6-benz-[4,5]-isoxazoloxy)propyloxy)phenylacetate, the title compound was obtained as a gum. NMR (CDCl₃) δ 0.959 (t, 3H); 1.07 (s, 9H); 1.69 (m, 2H); 2.37 (m, 2H); 2.82 (s, 2H); 2.87 (t, 2H); 3.61 (s, 2H); 3.85 (s, 3H); 4.27 (m, 4H); 6.83 (m, 2H); 6.94 (d, 1H); 6.95 (d, 1H); 7.37 (d, 1H). Mass spec, m/e = 470 (m + 1).

Example 66



3-(4-(2-(3-phenyl-7-propyl-6-benz-[4,5]-isoxazoloxy)ethyloxy))phenylpropionic acid

Step 1

The 6-(2-bromoeth-1-oxy)-3-phenyl-7-propylbenzisoxazole can be prepared as in Example 1 Step A from 6-hydroxy-3-phenyl-7-propylbenzisoxazole (1 g, 1.0 Eq, 4 mmol), prepared as described in Example 16 Step 3, and 1,2-dibromoethane (1.7 ml, 5 Eq, 20 mmol). The product was purified by elution from a silica gel column (44 g E. Merck 40-63 μ) with toluene : hexanes : EtOAc 30 : 65 : 5. Characteristic NMR Resonances; ¹H NMR 400MHz (CDCl₃); 7.92 (m, 2H), 7.65 (d, 1H, J = 8.7 Hz), 7.53 (m, 3H), 6.94 (d, 1H, J = 8.7 Hz),

- 146 -

4.39 (t, 2H, J = 6.1 Hz), 3.69 (t, 2H, J = 6.1 Hz), 2.94 (dd, 2H, J = 8.9, 7.5 Hz), 1.74 (sext, 2H, J = 7.5 Hz), 0.983 (t, 3H, J = 7.3 Hz).

MS ESI M+1 = 360 / 362.0. MW = 359.1 / 361.1

Step 2

The 6-(2-bromoeth-1-oxy)-3-phenyl-7-propylbenzisoxazole of example 67 Step 1 (47 mg, 1.0 Eq, 0.13 mmol) and commercially available methyl 3-(4-hydroxyphenyl)propionate (30 mg, 1.3 Eq, 0.16 mmol) were condensed as described in Example 16 Step 4. The product was purified by elution from a silica gel column (44 g E. Merck 40-63 μ) with toluene : hexanes : EtOAc 60 : 35 : 5.

Characteristic NMR Resonances; ^1H NMR 400MHz (CDCl_3); 7.92 (m, 2H), 7.66 (d, 1H, J = 8.7 Hz), 7.52 (m, 3H), 7.12 (d, 2H, J = 8.8 Hz & fine cplg), 7.02 (d, 1H, J = 8.8 Hz), 6.87 (d, 2H, J = 8.7 Hz & fine cplg.), 4.41 (complex m, 2H), 4.34 (complex m, 2H), 3.65 (s, 3H), 2.91 (t, 2H, J = 8.7 Hz), 2.89 (t, 2H, J = 8.1 Hz), 2.59 (dd, 2H, J = 8.1, 7.0 Hz), 1.71 (sext, 2H, 8.5 Hz), 0.939 (t, 3H, J = 7.4 Hz).

MS ESI M+1 = 460.3. MW = 459.2

Step 3

The ester of Example 66 Step 2 (34 mg, 1.0 Eq, 0.074 mmol) was hydrolyzed with LiOH (120 μL , 1.5 N, 2.3 Eq, 0.240 mmol) as described in Example 16 Step 5.

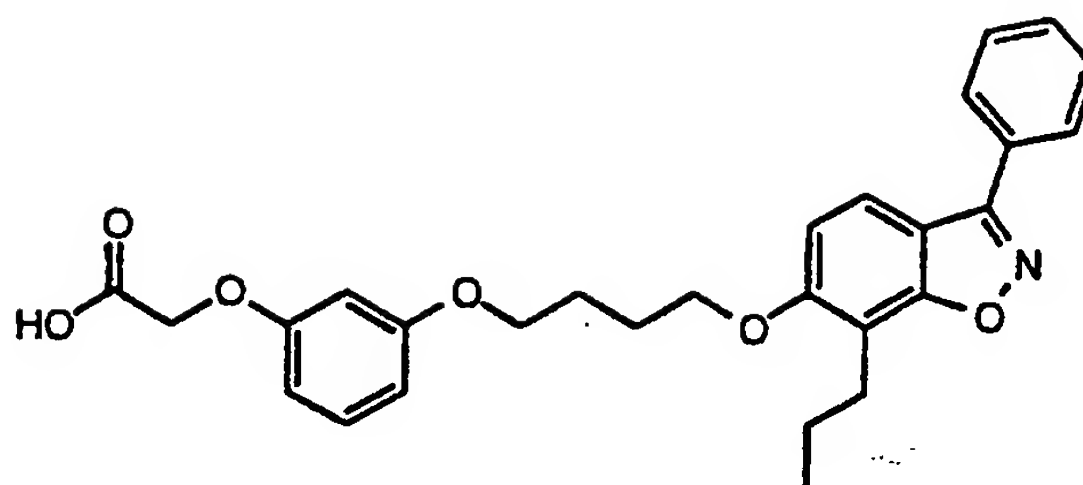
Characteristic NMR Resonances; ^1H NMR 400MHz (CDCl_3); 7.91 (m, 2H), 7.66 (d, 1H, J = 8.8 Hz), 7.51 (m, 3H), 7.14 (d, 2H, J = 8.8 Hz & fine spltg.), 7.02 (d, 1H, J = 8.8 Hz), 6.88 (d, 2H, J = 8.7 Hz & fine spltg.), 4.41 (m, 2H), 4.34 (m, 2H), 2.90 (m, 4H), 2.64 (t, 2H, J = 8.0 Hz), 1.71 (sext, 2H, J = 7.4 Hz), 0.938 (t, 3H, J = 7.4 Hz).

Analytical HPLC 75 : 25 CH_3CN : H_2O 0.1 % TFA, E. Merck RP-8 5 μ 4 X 250 mm, 1 ml/min. UV 210, RT 5.42 min.

MS ESI M+1 = 446.3. MW = 445.2.

Example 67

- 147 -



(3-(4-(3-phenyl-7-propyl-6-benz-[4,5]-isoxazoloxy)butyloxy))
phenoxyacetic acid

Step 1

Resorcinol (11 g, 4.0 Eq, 0.1 mol) and methyl α -bromoacetate (2.37 ml, 1.0 Eq, 0.025 mol) were combined in DMF (50 ml) with CsCO_3 (8.96 g, 1.1 Eq, 0.0275 mol). The mixture was stirred at RT 16 Hrs. The mixture was poured into 2 N HCl and EtOAc. The aqueous phase was extracted with EtOAc and the extracts washed with NaHCO_3 sat'd. aq. The extracts were dried over Na_2SO_4 and reduced *i. vac.* The product was purified by elution from a silica gel column (220 g E. Merck 40-63 μ) with toluene : EtOAc 82 : 18. Characteristic NMR Resonances; ^1H NMR 400MHz (CDCl_3); 7.12 (t, 1H), 6.4-6.46 (m, 2H), 4.60 (s, 2H), 3.79 (s, 3H).

Step 2

The 6-(4-bromobut-1-oxy)-3-phenyl-7-propylbenzisoxazole of Example 62 Step 1 (123 mg, 1.05 Eq, 0.316 mmol) and methyl 3-hydroxyphenoxyacetate of Example 67 Step 1 (50 mg, 1.0 Eq , 0.301 mmol) were condensed as described in Example 16 Step 4. The product was purified by elution from a silica gel column (10 g E. Merck 40-63 μ) with toluene : hexanes : EtOAc 50 : 45 : 5.

Characteristic NMR Resonances; ^1H NMR 400MHz (CDCl_3); 7.92 (m, 2H), 7.64 (d, 1H, $J = 8.7\text{Hz}$), 7.52 (m, 3H), 7.16 (t, 1H, $J = 8.2\text{ Hz}$), 6.97 (d, 1H, $J = 8.8\text{ Hz}$), 6.54 (dd, 1H, $J = 8.3, 2.3\text{ Hz}$), 6.46 (m, 2H), 4.60 (s, 2H), 4.14 (t, 2H, $J = 5.8\text{ Hz}$), 4.03 (t, 2H, $J = 5.8\text{ Hz}$), 3.78 (s, 3H), 2.91 (dd, 2H, $J = 8.7, 7.5\text{ Hz}$), 2.01 (m, 4H), 1.71 (sext, 2H, $J = 7.5\text{ Hz}$), 0.968 (t, 3H, $J = 7.4\text{ Hz}$).

- 148 -

MS ESI M+1 = 490.3. MW = 489.22.

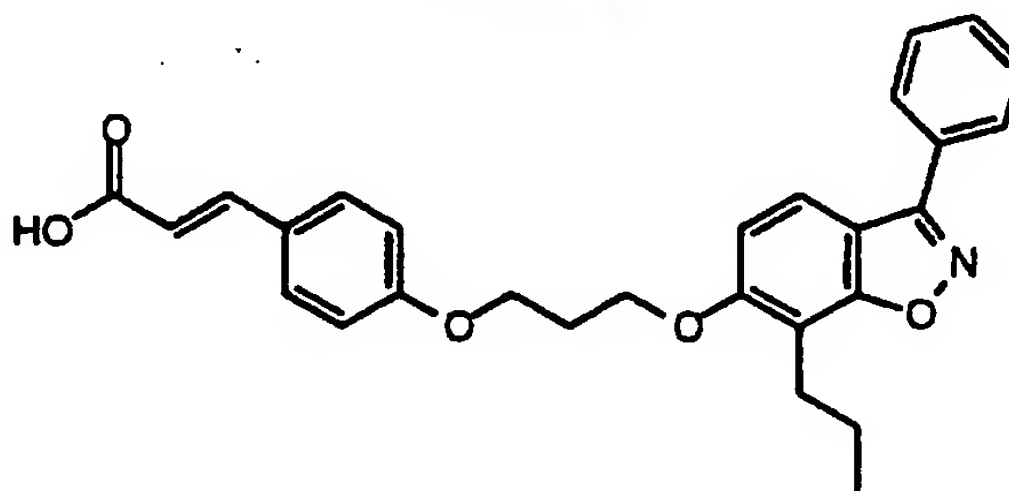
Step 3

The ester of Example 67 Step 2 (110 mg, 1.0 Eq, 0.225 mmol) was hydrolyzed with LiOH (299 μ L, 1.5 N, 2.0 Eq, 0.45 mmol) as described in Example 16 Step 5.

Characteristic NMR Resonances; ^1H NMR 400MHz (CDCl_3); 7.91 (m, 2H), 7.63 (d, 1H, $J = 8.8$ Hz), 7.51 (m, 3H), 7.18 (t, 2H, $J = 8.1$ Hz), 6.96 (d, 1H, $J = 8.8$ Hz), 6.57 (dd, 1H, $J = 7.5, 2.0$ Hz), 6.48 (m, 2H), 4.64 (s, 2H), 4.14 (t, 2H, $J = 5.6$ Hz), 4.02 (t, 2H, $J = 5.6$ Hz), 2.91 (dd, 2H, J unresolved), 2.02 (m, 4H), 1.71 (sext, 2H, $J = 7.5$ Hz), 0.964 (t, 3H, $J = 7.4$ Hz).

MS ESI M+1 = 476.3. MW = 475.2

Example 68



E-(4-(3-(3-phenyl-7-propyl-6-benz[4,5]isoxazole)oxy)propyloxy)cinnamic acid

Step 1

Commercially available 4-hydroxycinnamic acid (2 g) was esterified as described in Example 23 Step 1. The ester was used without purification further.

Characteristic NMR Resonances; ^1H NMR 400MHz (CDCl_3); 7.62 (d, 1H, $J = 16$ Hz), 7.41 (d, 2H, $J = 8.6$ Hz with fine splitting), 6.82 (d, 2H, $J = 8.6$ Hz with fine splitting), 6.28 (d, 1H, $J = 16$ Hz), 5.32 (s, 1H), 3.78 (s, 3H).

MS ESI M+1 = 179.1. MW = 178.2

- 149 -

Step 2

The 6-(3-bromoprop-1-oxy)-3-phenyl-7-propylbenzoxazole of Example 61 Step 1 (35.3 mg, 1.05 Eq, 0.85 mmol) and methyl 4-hydroxycinnamate of Example 68 Step 1 (16.3 mg, 1.6 Eq , 0.092 mmol) were condensed as described in Example 16 Step 4. The product was purified by elution from a silica gel column (2 g E. Merck 40-63 μ) with toluene : hexanes : EtOAc 60 : 35 : 5.

Characteristic NMR Resonances; ^1H NMR 400MHz (CDCl_3); 7.92 (m, 2H), 7.63 7.66 (overlapping d's, 2H), 7.53 (m, 3H), 7.47 (d, 1H, $J = 8.8$ Hz), 7.2 (m, 1H), 7.0 (d, 1H, $J = 8.8$ Hz), 6.92 (d, 1H, $J = 8.8$ Hz), 6.30 (d, 1H, $J = 16$ Hz), 4.29 (t, 2H, $J = 6.0$ Hz), 4.25 (t, 2H, $J = 6.1$ Hz), 3.79 (s, 3H), 2.92 (dd, 2H, J unresolved), 2.35 (m, 2H), 1.71 sext, 2H, $J = 7.5$ Hz), 0.96 (t, 3H, $J = 7.5$ Hz).

MS ESI $M+1 = 472.3$. MW = 471.2

Step 3

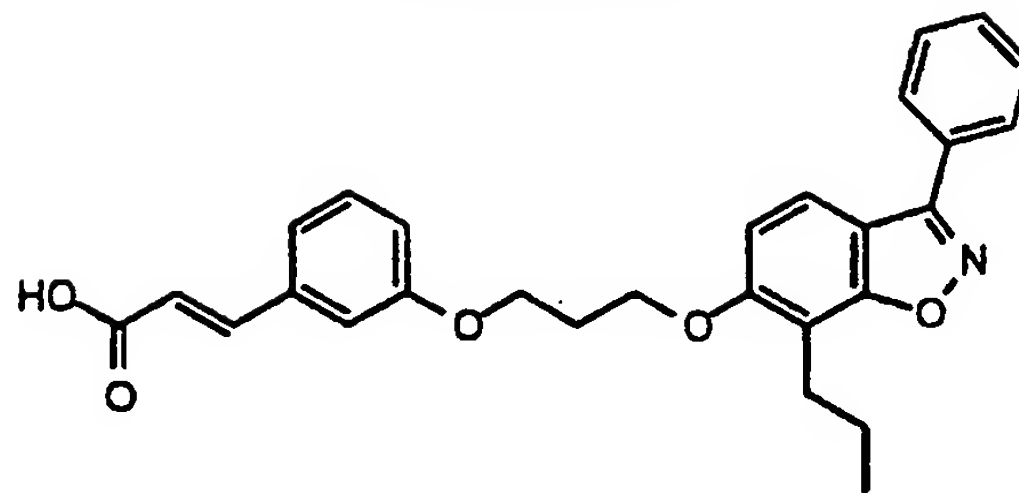
The ester of Example 68 Step 2 (25.9 mg, 1.0 Eq, 0.055 mmol) was hydrolyzed with LiOH (60 μL , 1.5 N, 2.2 Eq, 0.120 mmol) as described in Example 16 Step 5.

Characteristic NMR Resonances; ^1H NMR 400MHz (CDCl_3); 7.91 (m, 2H), 7.71 (d, 1H $J = 16$ Hz), 7.64 (d, 1H, $J = 8.7$ Hz), 7.51 (m, 3H), 7.0 (d, 1H, $J = 8.8$ Hz), 6.92 (d, 1H, $J = 8.9$ Hz plus fine coupling), 6.92 (d, 1H, $J = 16$ Hz), 4.28 (t, 2H, $J = 5.9$ Hz), 4.24 (t, 2H, $J = 6.2$ Hz), 2.91 (t, 2H, $J = 7.4$ Hz), 2.34 (m, 2H), 1.69 (sext, 2H, $J = 7.5$ Hz), 0.95 (t, 3H, $J = 7.4$ Hz).

Analytical HPLC 75 : 25 CH_3CN : H_2O 0.1 % TFA, E. Merck RP-8 5 μ 4 X 250 mm, 1 ml/min. UV 210, RT 6.63 min.

MS ESI $M+1 = 458.4$. MW = 457.2

- 150 -

Example 69

E-(3-(3-(3-phenyl-7-propyl-6-benz[4,5]isoxazole)oxy)propyloxy)cinnamic acid

Step 1

Commercially available 3-hydroxycinnamic acid (2 g) was esterified as described in Example 23 Step 1. The ester was used without purification further.

Characteristic NMR Resonances; ^1H NMR 400MHz (CDCl_3); 7.62 (d, 1H, $J = 16$ Hz), 7.24 (m, 1H), 7.70 (d, 1H, $J = 7.7$ Hz), 6.99 (m, 1H), 6.85 (dd, 1H, $J = 8.1, 2.1$ Hz), 6.39 (d, 1H, $J = 16$ Hz), 5.40 (s, 1H), 3.79 (s, 3H).

MS ESI $M+1 = 179.1$. MW = 178.1

Step 2

The 6-(3-bromoprop-1-oxy)-3-phenyl-7-propylbenzisoxazole of Example 61 Step 1 (31.4 mg, 1.0 Eq, 0.084 mmol) and methyl 3-hydroxycinnamate of Example 69 Step 1 (30 mg, 2.0 Eq, 0.169 mmol) were condensed as described in Example 16 Step 4. The product was purified by elution from a silica gel column (2 g E. Merck 40-63 μ) with toluene : hexanes : EtOAc 60 : 35 : 5.

Characteristic NMR Resonances; ^1H NMR 400MHz (CDCl_3); 7.92 (m, 2H), 7.66 (d, 1H $J = 16$ Hz), 7.67 (d, 1H, $J = 8.0$ Hz), 7.52 (m, 3H), 7.30 (t, 1H, $J = 7.8$ Hz), 7.11 (m, 1H), 7.05 (brd s, 1H), 7.01 (d, 1H, $J = 8.7$ Hz), 6.95 (dd, 1H), 6.42 (d, 1H, $J = 16$ Hz), 4.29 (t, 2H, $J = 6.0$ Hz), 4.24 (t, 2H, $J = 6.0$ Hz), 3.80 (s, 3H), 2.93 (t, 2H, $J = 7.2$ Hz), 2.35 (pent, 2H, $J = 5.8$ Hz), 1.71 (sext, 2H, $J = 7.4$ Hz), 0.96 (t, 3H, $J = 7.4$ Hz).

- 151 -

MS ESI M+1 = 472.3. MW = 471.2

Step 3

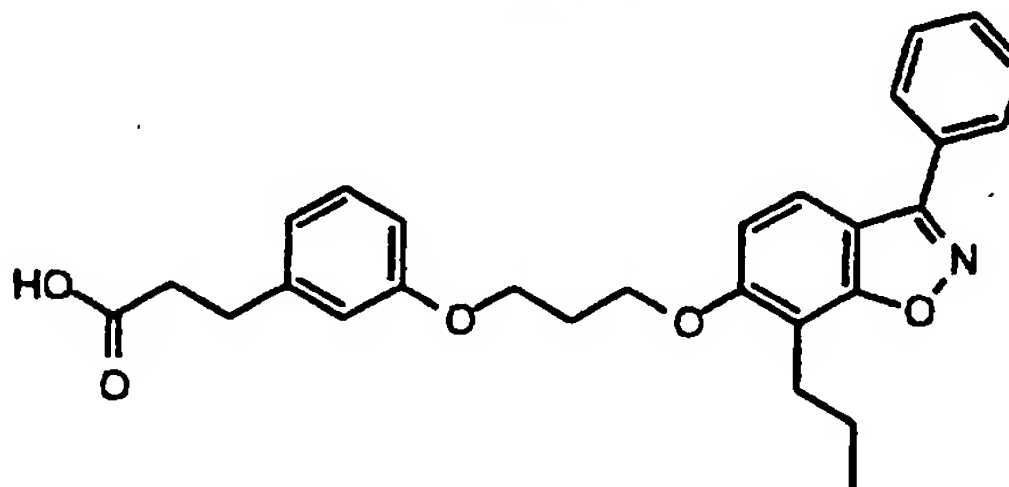
The ester of Example 69 Step 2 (27.7 mg, 1.0 Eq, 0.055 mmol) was hydrolyzed with LiOH (65 μ L, 1.5 N, 2.2 Eq, 0.131 mmol) as described in Example 16 Step 5.

Characteristic NMR Resonances; ^1H NMR 400MHz (CDCl_3); 7.92 (m, 2H), 7.72 (d, 1H, J = 16 Hz), 7.64 (d, 1H, J = 8.7 Hz), 7.52 (m, 3H), 7.30 (t, 1H, J = 8.0 Hz), 7.13 (m, 1H), 7.08 (brd s, 1H), 7.00 (d, 1H, J = 8.8 Hz), 6.96 (dd, 1H), 6.41 (d, 1H, J = 16 Hz), 4.29 (t, 2H, J = 6.0 Hz), 4.23 (t, 2H, J = 6.0 Hz), 2.91 (t, 2H, J = 7.5 Hz), 2.34 (pent, 2H), 1.69 (sext, 2H, J = 7.5 Hz), 0.95 (t, 3H, J = 7.3 Hz).

Analytical HPLC 75 : 25 CH_3CN : H_2O 0.1 % TFA, E. Merck RP-8 5μ 4 X 250 mm, 1 ml/min. UV 210, RT 6.89 min.

MS ESI M+1 = 458.3. MW = 457.2

Example 70



3-(3-(3-(3-phenyl-7-propyl-6-benz[4,5]isoxazole)oxy)propyloxy)phenylpropionic acid

Step 1

Methyl 3-hydroxycinnamate of Example 69 Step 1 (1.1 g, 1.0 Eq , 6.2 mmol) was hydrogenated at atmospheric pressure in EtOAc (45 ml) with 10 % Pd on carbon (98 mg) as catalyst. After complete consumption of the starting cinnamate, the hydrogenation mixture was filtered through celite and reduced *i. vac.* The ester was used without purification.

- 152 -

Characteristic NMR Resonances; ^1H NMR 400MHz (CDCl_3); 7.14 (dd, 1H, J unresolved), 6.75 (d, 1H, $J = 7.8$ Hz), 6.65 (m, 1H), 4.73 (s, 1H), 2.89 (t, 2H, $J = 7.5$ Hz), 2.60 (t, 2H, $J = 7.5$ Hz).
MS EI $M^+ = 180.1$. MW = 180.1

Step 2

The 6-(3-bromoprop-1-oxy)-3-phenyl-7-propylbenzisoxazole of Example 61 Step 1 (38.4 mg, 1.0 Eq, 0.103 mmol) and methyl 3-(3-hydroxyphenyl)propionate of Example 70 Step 1 (20 mg, 2.0 Eq , 0.111 mmol) were condensed as described in Example 16 Step 4. The product was purified by elution from a silica gel column (2 g E. Merck 40-63 μ) with toluene : hexanes : EtOAc 60 : 35 : 5.

Characteristic NMR Resonances; ^1H NMR 400MHz (CDCl_3); 7.92 (m, 2H), 7.66 (d, 1H, $J = 8.7$ Hz), 7.53 (m, 3H), 7.20 (m, 1H), 7.01 (d, 1H, $J = 8.7$ Hz), 6.78 (m, 3H), 4.29 (t, 2H, $J = 6.0$ Hz), 4.20 (t, 2H, $J = 6.0$ Hz), 3.66 (s, 3H), 2.92 (overlapping m's, 4H), 2.62 (t, 2H, $J = 7.5$ Hz), 2.33 (pent, 2H, $J = 6.3$ Hz), 1.71 (sext, 2H, $J = 7.5$ Hz), 0.97 (t, 3H, $J = 7.5$ Hz).

MS ESI $M+1 = 474.4$. MW = 473.2

Step 3

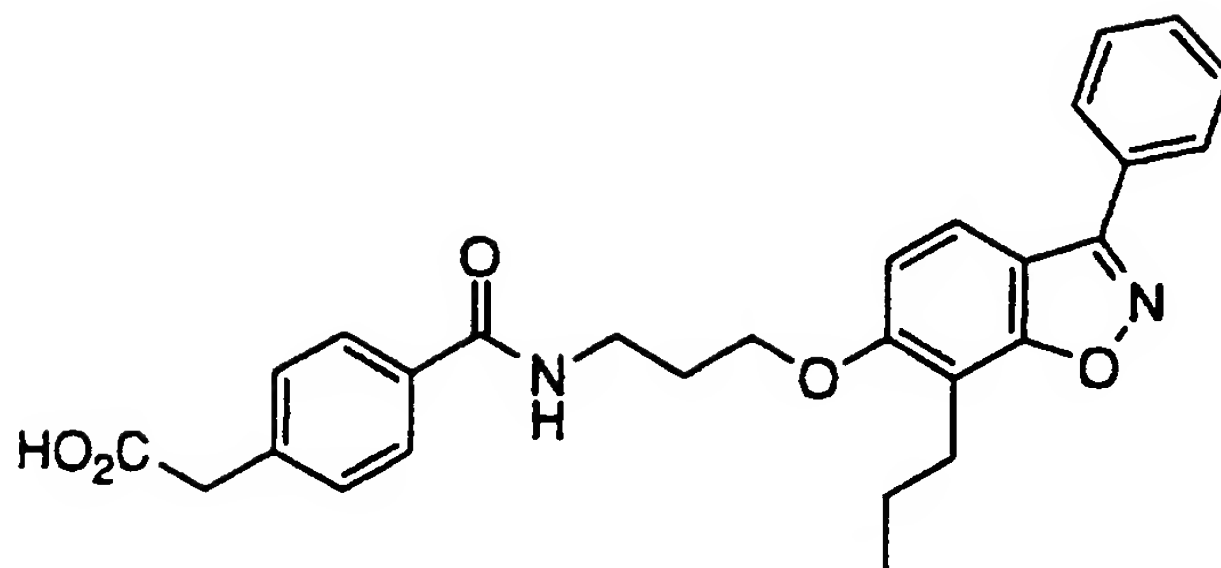
The ester of Example 70 Step 2 (32.7 mg, 1.0 Eq, 0.069 mmol) was hydrolyzed with LiOH (100 μL , 2.0 N, 2.9 Eq, 0.200 mmol) as described in Example 16 Step 5.

Characteristic NMR Resonances; ^1H NMR 400MHz (CDCl_3); 7.92 (m, 2H), 7.63 (d, 1H, $J = 8.7$ Hz), 7.52 (m, 3H), 7.19 (m, 1H), 6.99 (d, 1H, $J = 8.7$ Hz), 6.78 (m, 3H), 4.27 (t, 2H, $J = 6.0$ Hz), 4.18 (t, 2H, $J = 6.0$ Hz), 2.91 (overlapping t's, 4H), 2.65 (t, 2H, $J = 8.1$ Hz), 2.31 (pent, 2H, $J = 6.1$ Hz), 1.71 (sext, 2H, $J = 7.3$ Hz), 0.95 (t, 3H, $J = 7.4$ Hz).

Analytical HPLC 75 : 25 CH_3CN : H_2O 0.1 % TFA, E. Merck RP-8 5 μ 4 X 250 mm, 1 ml/min. UV 210, RT 6.55 min.

MS ESI $M+1 = 460.3$. MW = 459.2

- 153 -

Example 71

N-((4-carbomethoxymethyl)benzoyl)-3(3-phenyl-7-propyl-6-benz-[4,7]-isooxazolyloxy) propylamine

Step A: Preparation of 3-phenyl-6-(3-aminopropyl)oxy-7-propyl benz-[4,7]-isoxazole hydrochloride: 506 mg (2.0 mmole, 1.0 eq.) of 3-phenyl-6-hydroxy-7-propyl benz-[4,7]-isoxazole (example 16, step 3) was dissolved in 20 ml of freshly distilled tetrahydrofuran, after which 525 mg (2.0 mmole, 1.0 eq.) triphenylphosphine and 0.34 ml (2.0 mmole, 1.0 eq.) of *tert*-butyl N-(3-hydroxypropyl)carbamate were added with stirring. The reaction vessel was cooled to 0°C and 0.31 ml (2.0 mmole, 1.0 eq.) of diisopropyl azodicarboxylate was added dropwise. Once addition was complete the cooling bath was removed and the reaction was allowed to stir at room temperature for 24 hours. Saturated sodium bicarbonate solution was added to the stirring reaction mixture, which was then extracted with ethyl acetate. The ethyl acetate layer was washed with dilute HCl, dried over sodium sulfate, filtered and the filtrate evaporated. The residue was then treated with 10 ml of 4N HCl in dioxane (40 mmole, 20 eq.). After 20 minutes TLC shows Boc removal complete, so dioxane was evaporated and ether was added, upon which a precipitate formed. The suspension was stirred for 20 minutes, then filtered. The recovered solid was pumped on high vacuum to give 550 mg (79% yield) of the title compound.

- 154 -

¹H NMR (500 MHz, CD₃OD): δ 7.93 (m, 2H), 7.80 (d, 1H), 7.57 (m, 3H), 7.19 (d, 1H), 4.27 (t, 2H), 3.21 (t, 2H), 2.93 (t, 2H), 2.23 (m, 2H), 1.73 (m, 2H), 0.99 (t, 3H).

Step B: Preparation of N-((4-carbomethoxymethyl)benzoyl)-3(3-phenyl-7-propyl-6-benz-[4,7]-isooxazolyloxy) propylamine: 19.4 mg (0.10 mmole, 1.0 eq.) of the known compound methyl 4-carboxyphenyl acetate was dissolved in 1 ml dichloromethane, then treated with 21.1 mg (0.11 mmole, 1.1 eq.) of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride and 14.9 mg (0.11 mmole, 1.0 eq.) 1-hydroxybenzotriazole. After stirring together for 20 minutes, 34.7 mg (0.10 mmole, 1.0 eq) of 3-phenyl-6-(3-aminopropyl)oxy-7-propyl benz-[4,7]-isoxazole hydrochloride from Example 72 step A and 26 µl (0.15 mmole, 1.5 eq.) of diisopropylethylamine were added and the reaction stirred for 16 hours. The reaction mixture was then diluted with dichloromethane, washed twice each with 5% citric acid and 5% sodium bicarbonate solutions. The dichloromethane was then dried over sodium sulfate, filtered, evaporated and purified by silica gel chromatography to give 37 mg (76% yield) of the title compound.

¹H NMR (500 MHz, CDCl₃): δ 7.95 (dd, 2H), 7.74 (d, 2H), 7.68 (d, 1H), 7.55 (m, 3H), 7.35 (d, 2H), 7.01 (d, 1H), 6.45 (br t, 1H), 4.23 (t, 2H), 3.74 (q, 2H), 3.71 (s, 3H), 3.68 (s, 2H), 2.93 (t, 2H), 2.22 (m, 2H), 1.74 (m, 2H), 0.98 (t, 3H).

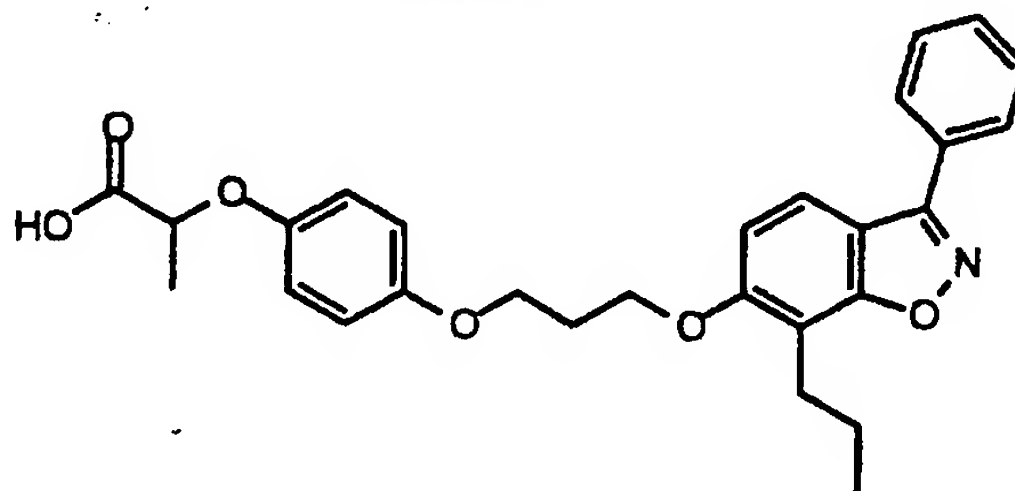
Step C: Preparation of N-((4-carboxymethyl)benzoyl)-3(3-phenyl-7-propyl-6-benz-[4,7]-isooxazolyloxy) propylamine: 10 mg (20.6 µmole, 1.0 eq.) of N-((4-carbomethoxymethyl)benzoyl)-3(3-phenyl-7-propyl-6-benz-[4,7]-isooxazolyloxy) propylamine from Example 72 step B was dissolved in 0.45 ml tetrahydrofuran and 0.25 ml of methanol. Then 0.15 ml of water and 0.10 ml of 0.25 N (25 µmole, 1.2 eq.) lithium hydroxide were added. The reaction was heated to 40°C and after two hours diluted with water, acidified and extracted twice with dichloromethane. The dichloromethane was dried over sodium sulfate, filtered and the filtrate evaporated to give the title compound.

- 155 -

^1H NMR (500 MHz, CDCl_3): δ 7.94 (dd, 2H), 7.73 (d, 2H), 7.65 (d, 1H), 7.55 (m, 3H), 7.34 (d, 2H), 6.99 (d, 1H), 6.56 (br t, 1H), 4.20 (t, 2H), 3.72 (q, 2H), 3.69 (s, 2H), 2.91 (t, 2H), 2.20 (m, 2H), 1.74 (m, 2H), 0.95 (t, 3H).

MS(ESI, TFA/ HCOONH_4): m/e 473.3 $[\text{M}+1]$.

Example 72



2-(4-(3-(3-phenyl-7-propyl-6-benz-[4,5]-isoxazoloxy)propyloxy))
phenoxypropionic acid

Step 1

The commercially available 2-(4-hydroxyphenoxy)propionic acid (2 g) was esterified as for Example 23 Step 1. The ester was used without purification.

Characteristic NMR Resonances; ^1H NMR 400MHz (CDCl_3); 6.75 (collapsed ABq, 4H), 4.66 (q, 1H, $J = 6.9$ Hz), 3.75 (s, 3H), 1.58 (d, 3H, $J = 6.9$ Hz).

MS CI NH_3 $\text{M}+\text{NH}_4^+ = 214.1$. MW = 196

Step 2

The 6-(3-bromoprop-1-oxy)-3-phenyl-7-propylbenzisoxazole of Example 61 Step 1 (31.7 mg, 1.0 Eq, 0.85 mmol) and methyl 2-(4-hydroxyphenoxy)propionate of Example 72 Step 1 (27 mg, 1.6 Eq , 0.138 mmol) were condensed as described in Example 16 Step 4.

The product was purified by elution from a silica gel column (2 g E. Merck 40-63 μ) with toluene : hexanes : EtOAc 60 : 35 : 5.

- 156 -

Characteristic NMR Resonances; ^1H NMR 400MHz (CDCl_3); 7.92 (m, 2H), 7.66 (d, 1H, $J = 8.7$ Hz), 7.53 (m, 3H), 7.00 (d, 1H, $J = 8.9$ Hz), 6.83 (s, 4H), 4.67 (q, 1H, $J = 6.8$ Hz), 4.28 (t, 2H, $J = 6.0$ Hz), 4.16 (t, 2H, $J = 6.0$ Hz), 3.75 (s, 3H), 2.92 (dd, 2H, $J = 8.7, 7.4$ Hz), 2.30 (pent, 2H, $J = 6.1$ Hz), 1.71 (sext, 2H, $J = 7.6$ Hz), 1.59 (d, 3H, $J = 6.8$ Hz), 0.97 (t, 3H, $J = 7.4$ Hz).

MS ESI $M+1 = 490.4$. MW = 489.2

Step 3

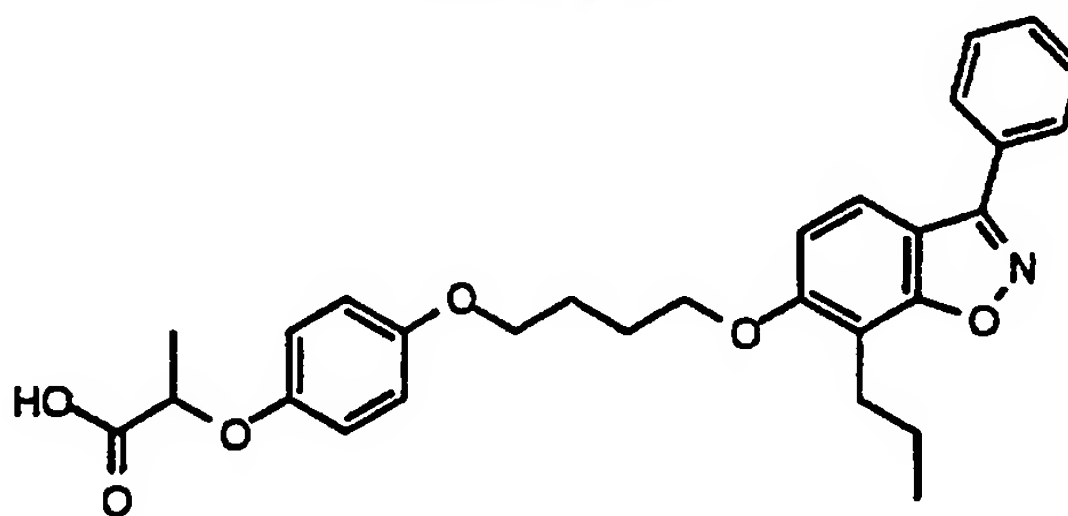
The ester of Example 72 Step 2 (29 mg, 1.0 Eq, 0.059 mmol) was hydrolyzed with LiOH (80 μL , 2.0 N, 2.7 Eq, 0.16 mmol) as described in Example 16 Step 5.

Characteristic NMR Resonances; ^1H NMR 400MHz (CDCl_3); 7.92 (m, 2H), 7.63 (d, 1H, $J = 8.8$ Hz), 7.51 (m, 3H), 6.98 (d, 1H, $J = 8.7$ Hz), 6.84 (s, 4H), 4.68 (q, 1H, $J = 6.9$ Hz), 4.26 (t, 2H, $J = 5.9$ Hz), 4.14 (t, 2H, $J = 6.0$ Hz), 2.89 (dd, 2H, J unresolved), 2.29 (pent, 2H, $J = 6.0$ Hz), 1.69 (sext, 2H, $J = 7.5$ Hz), 1.60 (d, 3H, $J = 6.8$ Hz), 0.94 (t, 3H, $J = 7.4$ Hz).

Analytical HPLC 75 : 25 $\text{CH}_3\text{CN} : \text{H}_2\text{O}$ 0.1 % TFA, E. Merck RP-8 5 μ 4 X 250 mm, 1 ml/min. UV 210, RT 6.09 min.

MS ESI $M+1 = 476.3$. MW = 475.2

Example 73



2-(4-(4-(3-phenyl-7-propyl-6-benz-[4,5]-isoxazoloxy)butyloxy))
phenoxypropionic acid

Step 1

- 157 -

The 6-(3-bromobut-1-oxy)-3-phenyl-7-propylbenzisoxazole of Example 62 Step 1 (37 mg, 1.2 Eq, 0.095 mmol) and methyl 2-(4-hydroxyphenoxy)propionate of Example 72 Step 1 (16 mg, 1.0 Eq , 0.082 mmol) were condensed as described in Example 16 Step 4. The product was purified by elution from a silica gel column (2 g E. Merck 40-63 μ) with toluene : hexanes : EtOAc 60 : 35 : 5.

Characteristic NMR Resonances; ^1H NMR 400MHz (CDCl_3); 7.92 (m, 2H), 7.65 (d, 1H, $J = 8.7$ Hz), 7.53 (m, 3H), 6.98 (d, 1H, $J = 8.7$ Hz), 6.83 (s, 4H), 4.67 (q, 1H, $J = 6.8$ Hz), 4.10 (t, 2H), 4.01 (t, 2H), 3.75 (s, 3H), 2.93 (dd, 2H, $J = 8.6, 7.4$ Hz), 2.02 (m, 4H), 1.73 (sext, 2H, $J = 7.5$ Hz), 1.59 (d, 3H, $J = 6.8$ Hz), 0.99 (t, 3H, $J = 7.4$ Hz).

MS ESI $M+1 = 504.5$. MW = 503.2

Step 2

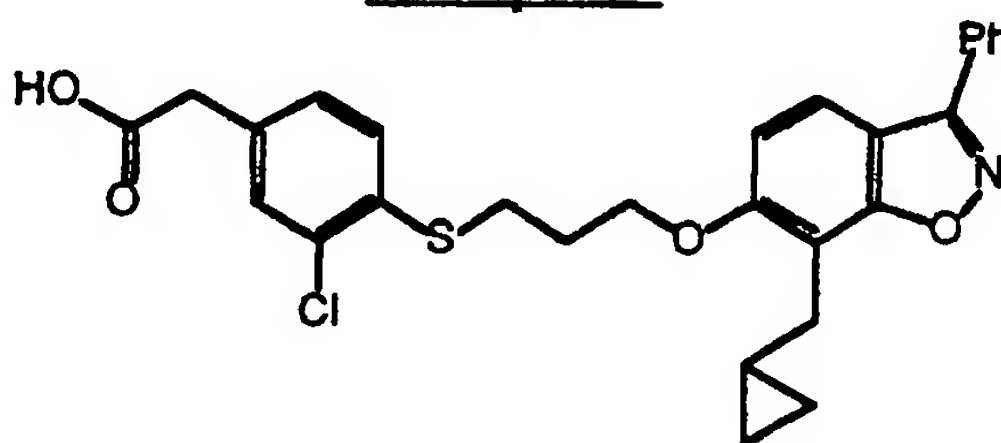
The ester of Example 73 Step 1 (35 mg, 1.0 Eq, 0.069 mmol) was hydrolyzed with LiOH (90 μL , 2.0 N, 2.6 Eq, 0.18 mmol) as described in Example 16 Step 5.

Characteristic NMR Resonances; ^1H NMR 400MHz (CDCl_3); 7.92 (m, 2H), 7.63 (d, 1H, $J = 8.7$ Hz), 7.53 (m, 3H), 6.96 (d, 1H, $J = 8.7$ Hz), 6.83 (collapsed ABq, 4H), 4.69 (q, 1H, $J = 6.9$ Hz), 4.14 (t, 2H, $J = 6.0$ Hz), 4.00 (t, 2H, $J = 6.0$ Hz), 2.90 (dd, 2H, $J = 8.7, 7.5$ Hz), 2.00 (m, 4H), 1.71 (sext, 2H, $J = 7.4$ Hz), 1.61 (d, 3H, $J = 6.8$ Hz), 0.96 (t, 3H, $J = 7.4$ Hz).

Analytical HPLC 75 : 25 $\text{CH}_3\text{CN} : \text{H}_2\text{O}$ 0.1 % TFA, E. Merck RP-8 5 μ 4 X 250 mm, 1 ml/min. UV 210, RT 6.84 min.

MS ESI $M+1 = 490.5$. MW = 489.2

Example 74



- 158 -

3-chloro-4-(3-(7-cyclopropylmethyl-3-phenyl-6-benz-[4, 5]-isoxazoloxy)propyl-thio)phenylacetic acid

STEP A: Preparation of 7-cyclopropylmethyl-3-phenyl-6-hydroxybenz-[4, 5]-isoxazole

Using the method and materials in example 24 the titled compound was obtained.

STEP B: Preparation of Methyl 3-chloro-4-(3-(7-cyclopropylmethyl-3-phenyl-6-benz-[4, 5]-isoxazoloxy)propyl-thio)phenylacetate

Using the method in example 20 step C (19632PV2), substituting 7-cyclopropylmethyl-3-phenyl-6-hydroxybenz-[4, 5]-isoxazole, the titled compound was obtained.

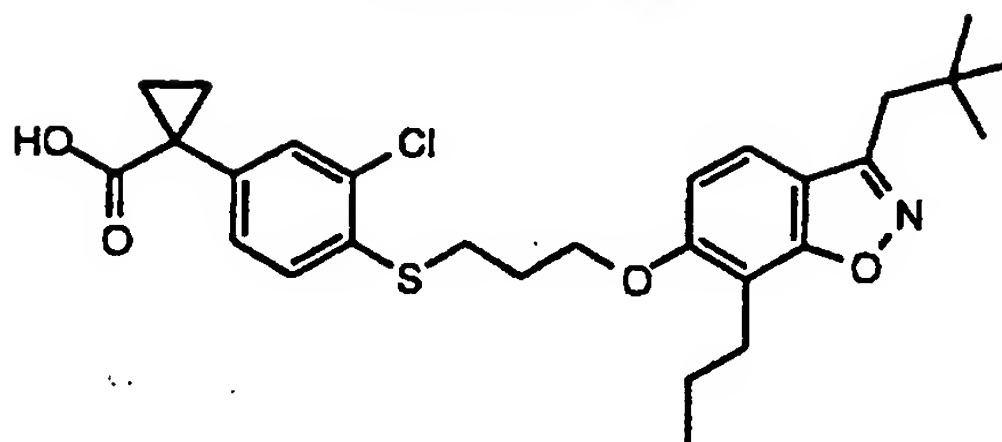
NMR (CDCl₃) δ 7.92 (m, 2H); 7.66 (d, 1H); 7.51 (m, 3H); 7.29 (m, 2H); 7.13 (d, 1H); 6.98 (d, 1H, J = 8.75 Hz); 4.22 (t, 2H, J = 5.78 Hz); 3.67 (s, 3H); 3.54 (s, 2H); 3.17 (t, 2H, J = 7.12 Hz); 2.86 (d, 2H, J = 6.87 Hz); 2.15 (m, 2H); 0.43 (m, 1H); 0.34 (m, 1H).

STEP C: Preparation of 3-chloro-4-(3-(7-cyclopropylmethyl-3-phenyl-6-benz-[4, 5]-isoxazoloxy)propyl-thio)phenylacetic acid

Using the method in example 2 step A THERE IS NO STEP A IN 19630PV2 OR 19632PV2, substituting Methyl 3-chloro-4-(3-(7-cyclopropylmethyl-3-phenyl-6-benz-[4, 5]-isoxazoloxy)propyl-thio)phenylacetate, the titled compound was obtained.

NMR (CDCl₃) δ 7.91 (m, 2H); 7.66 (d, 1H, J = 8.70 Hz); 7.52 (m, 3H); 7.29 (m, 2H); 7.14 (d, 1H, J = 1.89 Hz); 6.98 (d, 1H, J = 8.77 Hz); 4.22 (t, 2H, J = 5.78 Hz); 3.57 (s, 2H); 3.18 (t, 2H, J = 7.16 Hz); 2.86 (d, 2H, J = 6.75 Hz); 2.20 (m, 2H); 0.42 (m, 1H); 0.31 (m, 1H).

ESI: Mass spec: m/e = 508 (M+1).

Example 75

1-(3-chloro-4-(3-(3-(2,2-dimethylpropyl)-7-propyl-6-benz[4,5]isoxazole)oxy)propylthio) phenyl cyclopropane carboxylic acid

1. 3-(2,2-dimethylpropyl)-6-(3-bromopropoxy)-7-propylbenz[4,5]isoxazole

A solution of 3-(2,2-dimethylpropyl)-6-hydroxy-7-propylbenz[4,5] isoxazole (2.000 grams; 8.090 mmol) in dry DMF (20 mL) was treated with 1,3-dibromopropane (4.29 mL; 42.263 mmol). Cesium carbonate (2.900 grams; 8.901 mmol) was added and the mixture stirred at 20° for 8 hours. The reaction mixture was partitioned between isopropyl acetate and pH 4 buffer. The organic was washed with water, then dried over magnesium sulfate. Filtration and evaporation afforded an oil which was chromatographed over silica gel, giving the title compound.

NMR (CDCl₃): 7.37 (d, 1H, J = 8.8 Hz); 6.91 (d, 1H, J = 8.7 Hz); 4.19 (t, 2H, J = 5.6 Hz); 3.63 (t, 2H, J = 7.0 Hz); 2.86 (bt, 2H, J = 7.4 Hz); 2.80 (s, 2H); 1.03 (s, 9H).

2. 1-(3-chloro-4-(3-(3-(2,2-dimethylpropyl)-7-propyl-6-benz[4,5]isoxazole)oxy)propylthio)phenyl-1-cyclopropane carboxylic acid methyl ester

A solution of 1-(3-chloro-4-(3-(3-(2,2-dimethylpropyl)-7-propyl-6-benz[4,5]isoxazole)oxy)propylthio)phenyl-1-cyclopropane carboxylic acid methyl ester (0.059 grams; 0.188 mmol) in dry methanol (1 mL) was treated with a solution of sodium methoxide in methanol (4.37 M; 0.060 mL; 0.263 mmol). The solution was stirred at 60° C for 4 hours. The reaction was allowed to cool to 50° C and treated with 3-(2,2-dimethylpropyl)-6-(3-

- 160 -

bromopropoxy)-7-propylbenz[4,5]-isoxazole (0.083 grams; 0.226 mmol). The reaction was stirred for 2 hours more, then partitioned between isopropyl acetate and pH 4 buffer. The organic was dried over magnesium sulfate, filtered and evaporated to a residue which was chromatographed to afford the title compound.

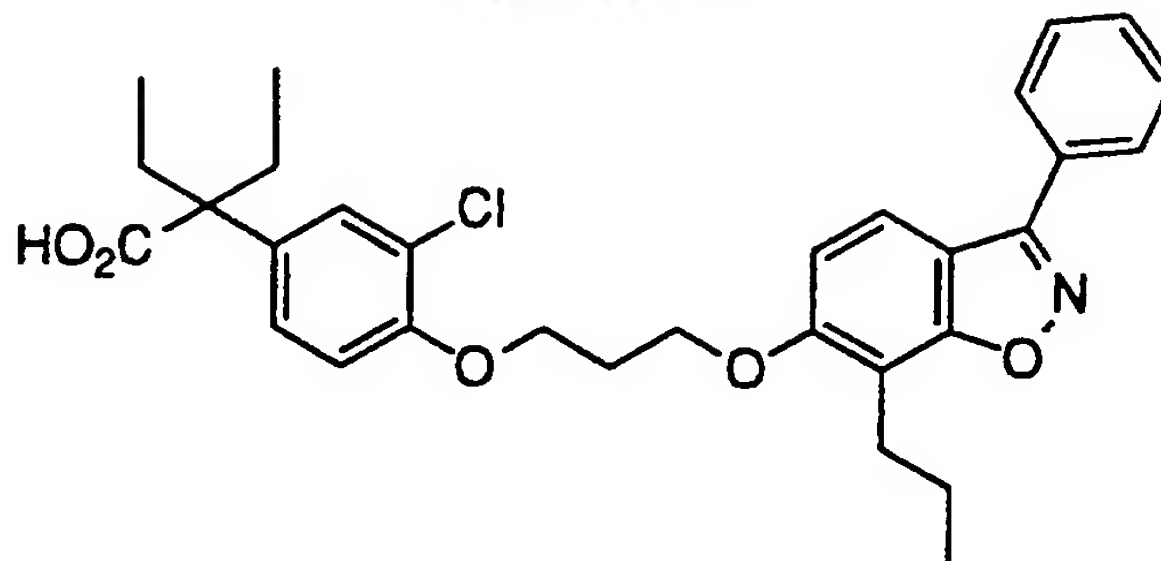
NMR (CDCl₃): 7.34 (d, 1H, J = 8.4 Hz); 7.33 (d, 1H, J = 1.8 Hz); 7.24 (d, 1H, J = 8.1 Hz); 7.16 (dd, 1H, J = 8.1, 1.9 Hz); 6.88 (d, 1H, J = 8.6 Hz); 4.17 (t, 2H, J = 5.8 Hz); 3.61 (s, 3H); 3.16 (t, 2H, J = 7.1 Hz); 2.86 (bt, 2H, J = 7.6 Hz); 2.79 (s, 2H); 1.59 (apparent quart, 2H, J = 3.7 Hz); 1.13 (apparent quart, 2H, J = 3.7 Hz); 1.03 (s, 9H).

3. 1-(3-chloro-4-(3-(3-(2,2-dimethylpropyl)-7-propyl-6-benz[4,5]isoxazole)oxy)propylthio)phenyl-1-cyclopropane carboxylic acid

A solution of 1-(3-chloro-4-(3-(3-(2,2-dimethylpropyl)-7-propyl-6-benz[4,5]isoxazole)oxy)propylthio)phenyl-1-cyclopropane carboxylic acid methyl ester (0.051 grams; 0.096 mmol) in isopropanol (2 mL) was refluxed. The solution was treated with a solution of KOH in water (1.00 M; 0.192 mL; 0.192 mmol). Refluxing was continued for 1 hour. The reaction was partitioned between isopropyl acetate and 0.1 N HCl. The organic was dried over magnesium sulfate, filtered and concentrated to the title compound as a solid.

NMR (CDCl₃): 7.34 (d, 1H, J = 8.4 Hz); 7.33 (d, 1H, J = 1.8 Hz); 7.24 (d, 1H, J = 8.1 Hz); 7.16 (dd, 1H, J = 8.1, 1.9 Hz); 6.88 (d, 1H, J = 8.6 Hz); 4.17 (t, 2H, J = 5.8 Hz); 3.61 (s, 3H); 3.16 (t, 2H, J = 7.1 Hz); 2.86 (bt, 2H, J = 7.6 Hz); 2.79 (s, 2H); 1.65 (apparent quart, 2H, J = 3.1 Hz); 1.20 (apparent quart, 2H, J = 3.3 Hz); 1.03 (s, 9H).

- 161 -

Example 76

4-(3-(3-(Ethyl)-7-(phenyl)-6-benz-[4,5]-isoxazoloxy)propyloxy)-3-chloro- α , α -dimethyl-phenyl propionic acid

Step A: Preparation of 3-chloro-(4-hydroxyphenyl)propionate:

In a 0°C ice bath, 3-chloro-(4-hydroxyphenyl)acetic acid (2.06 g; 11.0 mmol), was dissolved in 3 ml of ether. Added to this solution was about 35 mL of diazomethane dissolved in ether (0.32 mmol/mL). Allowed to stir for 5 minutes, vented the excess diazomethane to a colorless solution and concentrated *in vacuo* to afford a light yellow oil. Isolated 2.34 g of the title compound and used without further purification. NMR: δ 7.27 (m, 1H); 7.10 (m, 1H); 6.97 (d, 1H) 3.71 (s, 3H); 3.56 (s, 2H)

Step B: Preparation of 3-phenyl-7-propyl-6-(3-bromopropyl)oxy-benz-[4,5]-isoxazole

To a mixture of 3-phenyl-7-propyl-6-hydroxy-benz-[4,5]-isoxazole (1.0 g; 3.95 mmol, Prepared in Example 16 Step C), 1,3-dibromopropane (3.98g, 19.5 mmol) and potassium carbonate (0.573g, 4.15 mmol) in 4.0 mL of methyl ethyl ketone was warmed to reflux for 16 hours. Filtered, concentrated and chromatographed (silica gel, 30% ethyl acetate in hexane) to yield 1.025 g of the title compound as a white solid. NMR (CDCl₃): δ 7.95 (d, 2H); 7.69 (d, 1H); 7.55 (m, 3H); 7.03 (d, 1H); 4.25 (t, 2H); 3.68 (t, 2H); 2.95 (t, 2H); 2.41 (m, 2H); 1.76 (m, 2H); 1.01 (t, 3H)

- 162 -

Step C: Preparation of 4-(3-(3-(Ethyl)-7-(phenyl)-6-benz-[4,5]-isoxazoloxy)propyloxy)-3-chloro-phenyl propionate

A mixture of 3-chloro-(4-hydroxyphenyl)propionate (301.9 mg; 1.51 mmol), 3-(3-(Ethyl)-7-(phenyl)-6-benz-[4,5]-isoxazoloxy)-propyloxy bromide (540.2 mg; 1.66 mmol), cesium carbonate (514.0 mg; 1.58 mmol) in about 10.0 ml dry dimethyl-formamide was stirred and heated for 1.5 hours. Concentrated, diluted with water and extracted with ethyl acetate, dried (Na₂SO₄), concentrated *in vacuo* and chromatographed (silica gel, 30% ethyl acetate in hexane) to yield 633.4 mg of the title compound as a light yellow oil. NMR (CDCl₃): δ 7.95 (d,2H); 7.67 (d,1H); 7.54 (m,3H); 7.31 (s,1H); 7.14 (q,1H); 7.05 (d,1H); 6.93 (d,1H); 4.35 (t,2H); 4.27 (t,2H); 4.13 (t,2H); 3.70 (s,3H); 3.55 (s,2H); 2.93 (t,2H); 2.38 (m,2H)

Step D: Preparation of 4-(3-(3-(Ethyl)-7-(phenyl)-6-benz-[4,5]-isoxazoloxy)propyloxy)-3-chloro- α -methyl-phenyl propionate

To a solution of 4-(3-(3-(Ethyl)-7-(phenyl)-6-benz-[4,5]-isoxazoloxy)propyloxy)-3-chloro-phenyl propionate (148.0 mg; 0.332 mmol) in ca. 2.0 ml of dry tetrahydrofuran in a -78°C ice bath under nitrogen was added hexamethyl-disilylazid (0.5 M solution in toluene, 730 μ L; 0.365 mmol) and stirred for 30 minutes. To this solution was added iodoethane (53.1 μ L; 0.664 mmol) and was allowed to warm to room temperature and stir for 1 hour. The solution was quenched with 1 M(aq) NH₂Cl and washed with water and extracted with ethyl acetate, dried (Na₂SO₄) and concentrated *in vacuo* and chromatographed (silica gel 30% ethyl acetate) to yeild 32.1 mg of the title compound as a colorless oil. NMR (CDCl₃): δ 7.95 (d,2H); 7.68 (d,1H); 7.55 (m,3H); 7.33 (s,1H); 7.16 (d,1H); 7.07 (d,1H); 6.93 (d,1H); 4.35 (t,2H); 4.28 (t,2H);

Step E: Preparation of 4-(3-(3-(Ethyl)-7-(phenyl)-6-benz-[4,5]-isoxazoloxy)propyloxy)-3-chloro- α , α -dimethyl-phenyl propionate

The title compound was prepared by following the procedures in Example 1, step G affording 30.0 mg of viscous oil.

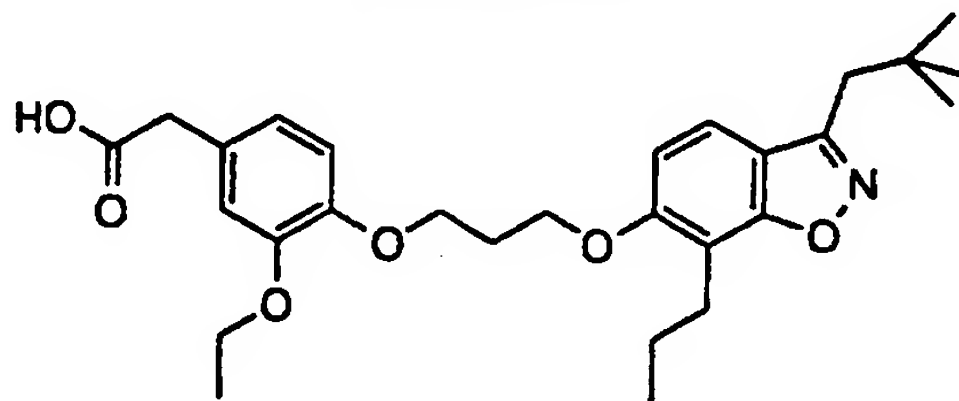
- 163 -

NMR (CDCl₃): δ 7.95 (d,2H); 7.67 (d,1H); 7.56 (m,4H); 7.41 (d,1H); 7.05 (d,1H); 6.94 (d,1H); 4.36 (t,2H); 4.30 (t,2H); 3.79 (s,3H);

Step F: Preparation of 4-(3-(3-(Ethyl)-7-(phenyl)-6-benz-[4,5]-isoxazoloxy)propyloxy)-3-chloro- α , α -dimethyl-phenyl propionic acid

A solution of 29.0 mg (0.0526 mmol) 4-(3-(3-(Ethyl)-7-(phenyl)-6-benz-[4,5]-isoxazoloxy)propyloxy)-3-chloro- α , α -dimethyl-phenyl propionate ca. 2.0 ml of isopropyl alcohol and 1 M aqueous potassium hydroxide (210 μ L; 4 eq) was heated at 60°C for 36 hours. The mixture was diluted with ethyl acetate and acidified to pH 5-6 with 1 M HCl, washed with water (2 times), brine (1 time) and dried over sodium sulfate, concentrated *in vacuo* and preparatory plate chromatography (silica 30% ethyl acetate in hex) to afford 20.0 mg of the title compound. (Mass Spec= 536.3, calc= 535.2); NMR (CDCl₃): δ 7.92 (d,2H); 7.63 (d,1H); 7.51 (m,4H); 6.99 (d,1H); 6.80 (d,1H); 4.29 (t,2H); 4.29 (t,2H); 3.46 (s,1H); 2.90 (t,2H); 2.32 (t,2H)

Example 77



3-Ethoxy-4-(3-(3-(2,2-dimethylpropyl)-7-propyl-6-benz-[4,5]-isoxazoloxy)propyloxy)phenylacetate

Step A: Preparation of methyl 3-ethoxy-4-(3-(3-(2,2-dimethylpropyl)-7-propyl-6-benz-[4,5]-isoxazoloxy)propyloxy)benzoate

Using the method of Example 56, Step D, and substituting 3-(2,2-dimethylpropyl)-6-(3-bromopropyloxy)-7-propyl-6-benz-[4,5]-isoxazole (Example 65, Step A) and methyl 4-hydroxy-3-ethoxybenzoate as starting materials, the title compound was obtained as an oil. NMR (CDCl₃): δ 0.95 (t, 3H); 1.07 (s, 9H); 1.45 (t, 3H); 1.70

- 164 -

(m, 2H); 2.40 (m, 2H); 2.82 (s, 2H); 2.88 (t, 2H); 3.90 (s, 3H); 4.13 (q, 2H); 4.12 (t, 2H); 4.13 (t, 2H); 6.93 (d, 1H); 6.94 (d, 1H); 7.37 (d, 1H); 7.56 (s, 1H); 7.66 (d, 1H).

Step B: Preparation of 3-ethoxy-4-(3-(3-(2,2-dimethylpropyl)-7-propyl-6-benz-[4,5]-isoxazoloxy)propyloxy)benzoate

Using the method of Example 37, Step E and substituting methyl 3-ethoxy-4-(3-(3-(2,2-dimethylpropyl)-7-propyl-6-benz-[4,5]-isoxazoloxy)propyloxy)benzoate, the title compound was obtained as an oil. NMR (CDCl₃); δ 0.96 (t, 3H); 1.07 (s, 9H); 1.46 (t, 3H); 1.69 (m, 2H); 2.40 (m, 2H); 2.83 (s, 2H); 2.88 (t, 2H); 4.14 (q, 2H); 4.31 (t, 2H); 4.34 (t, 2H); 6.96 (d, 2H); 7.38 (d, 1H); 7.6 (s, 1H); 7.75 (d, 1H).

Step C: Preparation of methyl 3-ethoxy-4-(3-(3-(2,2-dimethylpropyl)-7-propyl-6-benz-[4,5]-isoxazoloxy)propyloxy)phenylacetate

To a solution of 3-ethoxy-4-(3-(3-(2,2-dimethylpropyl)-7-propyl-6-benz-[4,5]-isoxazoloxy)propyloxy)benzoate (184 mg, 0.392 mmole) in methylene chloride (2 mL) and DMF (2 drops) at 0°C was added oxalyl chloride (36 μ L, 0.411 mmole). The mixture was stirred at room temperature for 30 minutes and then concentrated *in vacuo*. The residue was concentrated *in vacuo* 3x from methylene chloride. The final residue was dissolved in ether (5 mL) and treated with excess diazomethane in ether until the yellow color persisted. The yellow solution was stirred at room temperature for 3 hours. Nitrogen was bubbled through the solution for 5 minutes before concentrating *in vacuo*. The residue was dissolved in ethyl acetate and washed with 1N sodium bicarbonate, water, brine, dried over magnesium sulfate and concentrated *in vacuo* to give a yellow oil. The oil was dissolved in methanol (4 mL) and triethylamine (850 μ L) and stirred with silver benzoate (37 mg, 0.16 mmole) at room temperature for 18 hours. Celite and brine were added and the mixture was filtered, washing with methanol. The filtrate was concentrated *in vacuo* and the residue partitioned with ethyl acetate and 1N HCl. The organic phase was washed with water, brine, dried over magnesium sulfate and

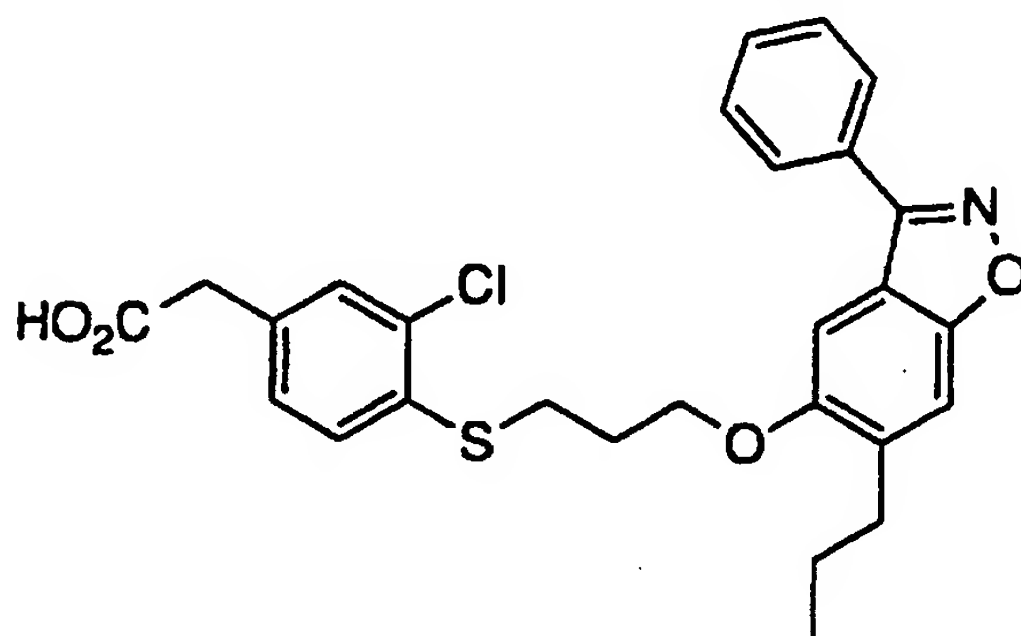
- 165 -

concentrated *in vacuo* to give an oil. Thin layer chromatography on silica gel eluting with hexane:2-propanol (9:1) provided the crude title compound (104 mg). A second thin layer chromatography on silica gel eluting with ethyl acetate:hexane (15:85) afforded the title compound (30 mg) as an oil. NMR (CDCl₃); δ 0.96 (t, 3H); 1.07 (s, 9H); 1.41 (t, 3H); 1.69 (m, 2H); 2.35 (m, 2H); 2.82 (s, 2H); 2.87 (t, 2H); 3.56 (s, 2H); 3.70 (s, 3H); 4.06 (q, 2H); 4.25 (t, 2H); 4.29 (t, 2H); 6.80 (d, 1H); 6.83 (d, 1H); 6.88 (d, 1H); 6.95 (d, 1H); 7.37 (d, 1H).

Step D: Preparation of 3-ethoxy-4-(3-(3-(2,2-dimethylpropyl)-7-propyl-6-benz-[4,5]-isoxazoloxy)propyloxy)phenylacetate

Using the method of Example 37, Step E and substituting methyl 3-ethoxy-4-(3-(3-(2,2-dimethylpropyl)-7-propyl-6-benz-[4,5]-isoxazoloxy)propyloxy)phenylacetate, the title compound was obtained as a gum. NMR (CDCl₃) δ 0.95 (t, 3H); 1.07 (s, 9H); 1.41 (t, 3H); 1.69 (m, 2H); 2.35 (m, 2H); 2.82 (s, 2H); 2.87 (t, 2H); 3.59 (s, 2H); 4.07 (q, 2H); 4.25 (t, 2H); 4.29 (t, 2H); 6.82 (d, 1H); 6.87 (d, 1H); 6.95 (d, 1H); 7.37 (d, 1H). Mass spec, $m/e = 484 (m + 1)$.

Example 78



3-chloro-4-(3-(3-phenyl-6-propyl-5-benz-[4,7]-isoxazolyloxy)-propylthio) phenylacetic acid

- 166 -

Step A: Preparation of 3-phenyl-5-hydroxy-6-propyl benz-[4,7]-isoxazole: 245 mg (0.90 mmole, 1.0 eq.) of 2,5-dihydroxy-4-propyl benzoxime from example 25, step G was dissolved in 5 ml acetic anhydride and allowed to stir 8 hours. The acetic anhydride was removed by high vacuum rotary evaporation and pumped on high vacuum for 16 hours. The crude material was then taken up in 3 ml pyridine and refluxed for 8 hours. Water and 2N HCl were added and the aqueous was extracted with ethyl acetate. The organic was dried over sodium sulfate, filtered and the filtrate evaporated. The residue was purified by silica gel chromatography to give 74.1 mg (32% yield) of the title compound, which was assigned after ¹H NMR, NOE difference spectroscopy, and mass spectrometry.

¹H NMR (500 MHz, CDCl₃): δ 7.93 (m, 2H), 7.54 (m, 3H), 7.42 (s, 1H), 7.26 (s, 1H), 2.77 (t, 2H), 1.75 (m, 2H), 1.05 (t, 3H).

MS (ESI, TFA/HCOONH₄): m/e 254.1 [M+1].

Step B: Preparation of methyl 4-(1-oxo-2-amino-5-(3-phenyl-7-propyl-6-benz-[4,7]-isoxazolyloxy)pentyl) phenyl acetate: 20 mg (79 μmole, 1.0 eq.) of 3-phenyl-5-hydroxy-6-propyl benz-[4,7]-isoxazole from Example 78 step A was dissolved in 0.75 ml of N,N-dimethylformamide. 27 mg (83 μmole, 1.05 eq.) of cesium carbonate and 26.7 mg (79 μmole, 1.0 eq.) of methyl 3-chloro-4-(3-bromopropylthio) phenyl acetate (example 25, step I) were then added and the reaction stirred at 60°C for 200 minutes. The reaction was cooled to room temperature, diluted with water and ethyl acetate, then acidified with dilute aqueous HCl. The organic layer was dried over sodium sulfate, filtered and the filtrate evaporated. The crude material was purified by preparative TLC to give the title compound.

¹H NMR (400 MHz, CDCl₃): δ 7.89 (m, 2H), 7.53 (m, 3H), 7.40 (s, 1H), 7.29 (d, 1H), 7.27 (d, 1H), 7.13 (s, 1H), 7.10 (dd, 1H), 4.14 (t, 2H), 3.68 (s, 3H), 3.52 (s, 2H), 3.18 (t, 2H), 2.74 (t, 2H), 2.21 (m, 2H), 1.66 (m, 2H), 0.98 (t, 3H).

- 167 -

Step C: Preparation of 4-(1-oxo-2-amino-5-(3-phenyl-7-propyl-6-benz-[4,7]-isoxazolyloxy)pentyl) phenylacetic acid: 14.2 mg (28 μ mole, 1.0 eq.) of methyl 4-(1-oxo-2-amino-5-(3-phenyl-7-propyl-6-benz-[4,7]-isoxazol-yloxy)pentyl) phenyl acetate from step B was dissolved in 0.4 ml of 1:1 tetrahydrofuran:methanol and 0.14 ml of 0.25 N (35 μ mole, 1.25 eq.) of lithium hydroxide and allowed to stir for 16 hours. The reaction mixture was then diluted with water, acidified with dilute aqueous HCl, and extracted with ethyl acetate. The organic layer was dried over sodium sulfate, filtered and the filtrate evaporated. The residue was purified by silica gel chromatography to give 10 mg (73% yield) of the title compound.

^1H NMR (500 MHz, CDCl_3): δ 7.93 (m, 2H), 7.57 (m, 3H), 7.43 (s, 1H), 7.33 (d, 1H), 7.29 (d, 1H), 7.15 (s, 1H), 7.13 (dd, 1H), 4.17 (t, 2H), 3.60 (s, 2H), 3.21 (t, 2H), 2.77 (t, 2H), 2.24 (m, 2H), 1.70 (m, 2H), 1.00 (t, 3H).

MS (ESI, TFA/ HCOONH_4): m/e 496.3 [M+1].

BIOLOGICAL ASSAYS

I. White Adipose Tissue *in vitro* Assay

The ability of compounds of the present invention to enhance the insulin activation of ^{14}C -glucose incorporation into glycogen in white adipose tissue (WAT) was determined by the following assay.

This assay measures the efficacy of the instant compounds to enhance the insulin activation of ^{14}C -glucose incorporation into glycogen in white adipose tissue (WAT) in a 5 hour completely *in vitro* system. All procedures are performed in medium 199 containing 1% bovine serum albumen, 5 mM HEPES, and antibiotic (100 units/ml penicillin, 100 $\mu\text{g}/\text{ml}$ streptomycin sulfate, 0.25 $\mu\text{g}/\text{ml}$ amphotericin B), hereafter called culture medium. Epididymol fat pads are minced with scissors into small fragments, approximately 1 mm in diameter. Minced WAT fragments (100 mg) are incubated in a total volume of 0.9 ml culture medium containing 1 mU/ml insulin and test compound in

- 168 -

tissue culture incubator at 37°C with 5% CO₂ with orbital shaking for 3 hours. ¹⁴C-labeled glucose is added and incubation continued for 2 hours. Tubes are centrifuged at low speed, infranatant is removed and 1 M NaOH is added. Incubation of alkali-treated WAT for 10 minutes at 60°C solubilizes tissue. Resulting tissue hydrolyzate is applied to Whatman filter paper strips which are then rinsed in 66% ethanol followed by 100% acetone which removes unincorporated ¹⁴C-glucose from bound ¹⁴C-glycogen. The dried paper is then incubated in solution of amyloglucosidase to cleave glycogen into glucose. Scintillation fluid is added and samples are counted for ¹⁴C activity. Test compounds that resulted in ¹⁴C activity substantially above incubations with insulin alone are considered active insulin-enhancing agents. Active compounds were titrated to determine the compound concentration which resulted in 50% of maximum enhancement of insulin activation and were termed EC₅₀ values. EC₅₀ values for the instant compounds were found to be 50 μM or less, preferably 5.0 to .0001 μM or less.

II. PPAR Receptor Binding and/or Transactivation Assays

Compounds of the instant invention which are useful for the above discussed treatments can be identified and/or characterized by employing the PPAR δ, and γ binding assays and/or PPAR δ, PPAR α and PPARγ transactivation assays. The assays are useful in predicting or quantitating in vivo effects having to do with the control or modulation of glucose, free fatty acid, triglyceride, insulin or cholesterol. To evaluate IC₅₀ or EC₅₀ values the compounds were titrated in the appropriate assay using different concentrations of the compound to be tested. To obtain the appropriate values (%Inhibition-IC₅₀, or %Activation-EC₅₀), the data resulting from the assays were then analyzed by determining the best fit of a 4 parameter function to the data using the Levenberg-Marquardt non-linear fitting algorithm in Kaleidagraph (Synergy Software, Reading, PA). The human nuclear receptor cDNA for PPARδ (hPPARδ) has been cloned from a human osteosarcoma cell cDNA library and is fully described in A. Schmidt et

- 169 -

al., Molecular Endocrinology, 6:1634-1641 (1992), herein incorporated by reference in its entirety. See A. Elbrecht et al., Biochem. and Biophys. Res. Comm. 224:431-437 (1996) and T. Sher et al., Biochem. 32:5598-5604 (1993) for a description of the human nuclear receptor gene PPAR γ and α .

The hPPAR δ binding assay comprises the steps of:

- (a) preparing multiple test samples by incubating separate aliquots of the receptor hPPAR δ with a test compound in TEGM containing 5-10% COS-1 cell cytoplasmic lysate and 2.5 nM labeled ($[^3\text{H}]$ Compound D, 17 Ci/mmol) for a minimum of 12 hours, and preferably for about 16 hours, at 4 °C, wherein the concentration of the test compound in each test sample is different, and preparing a control sample by incubating a further separate aliquot of the receptor hPPAR δ under the same conditions but without the test compound; then
- (b) removing unbound ligand by adding dextran/gelatin-coated charcoal to each sample while maintaining the samples at 4 °C and allowing at least 10 minutes to pass, then
- (c) subjecting each of the test samples and the control sample from step (b) to centrifugation at 4 °C until the charcoal is pelleted; then
- (d) counting a portion of the supernatant fraction of each of the test samples and the control sample from step (c) in a liquid scintillation counter and analyzing the results to determine the IC₅₀ of the test compound.

In the hPPAR δ binding assay, preferably at least four test samples of varying concentrations of a single test compound are prepared in order to determine the IC₅₀.

The hPPAR δ transactivation assay comprises the steps of:

- (a) seeding an hPPAR δ /GR stable CHO-K1 cell line into alpha MEM containing 10% FCS, 10 mM HEPES, and 500 mg/ml G418 at 37°C in an atmosphere of 10% CO₂ in air,
- (b) incubating the cells from step (a) for 16 to 48 hours, preferably about 20 hours, at 37°C in an atmosphere of 10% CO₂ in air;
- (c) washing the cells from step (b) with alpha MEM;

- 170 -

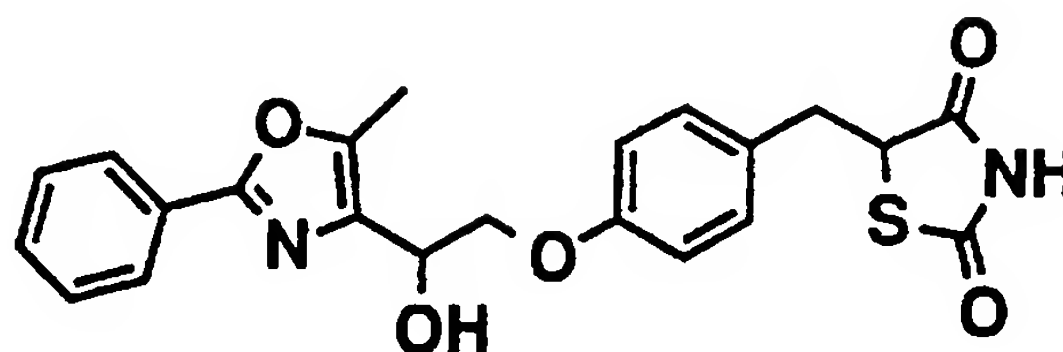
- (d) preparing multiple test cell groups by incubating separate groups of the cells from step (c) with the test compound in alpha MEM containing 5% charcoal stripped FCS, 10 mM HEPES, and 500 mg/ml G418, for 24 to 48 hours, preferably about 24 hours, at 37°C in an atmosphere of 10% CO₂ in air, wherein the concentration of the test compound in each test cell group is different, and preparing a control cell group by incubating a further separate group of the cells from step (c) under the same conditions but without the test compound; then
- (e) preparing cell lysates from each of the test cell groups and the control cell group of step (d) using an aqueous detergent lysis buffer, and
- (f) measuring the luciferase activity of the test cell groups and the control cell group of step (e) and analyzing the results to determine the EC₅₀ of the test compound.

In the hPPAR δ transactivation assay, preferably at least four test cell groups of varying concentrations of a single test compound are prepared in order to determine the EC₅₀.

Particular terms and abbreviations used herein are defined as follows: gst is glutathione-S-transferase; EDTA is ethylenediamine-tetraacetic acid; HEPES is N-[2-hydroxyethyl]-piperazine-N'-[2-ethanesulfonic acid]; FCS is fetal calf serum; Lipofectamine is a 3:1 (w/w) liposome formulation of the polycationic lipid 2,3-dioleoyloxy-N-[2(spermine-carboxamido)ethyl]-N,N-dimethyl-1-propanaminium-trifluoroacetate and the neutral lipid dioleoyl phosphatidylethanolamine in water; G418 is geneticin; MEM is Minimum Essential Medium; Opti MEM 1 Reduced-Serum Medium is an aqueous composition containing HEPES buffer, 2400 mg/L sodium bicarbonate, hypoxanthine, thymidine, sodium pyruvate, L-glutamine, trace elements, growth factors, and phenol red reduced to 1.1 mg/L; Luciferase Assay Reagent (in re-constituted form) is an aqueous composition containing 20 mM tricine, 1.07 mM (MgCO₃)₄Mg(OH)₂•5H₂O, 2.67 mM MgSO₄, 0.1 mM EDTA, 33.3 mM DTT, 270 μ M coenzyme A, 470 μ M luciferin, 530 μ M ATP, having a final pH of 7.8.

- 171 -

AD-5075 has the following structure:



AD-5075 (Takeda)

Opti MEM 1 Reduced-Serum Medium, alpha MEM, G418, and Lipofectamine are commercially available from GibcoBRL Life Technologies, Gaithersburg, Maryland. Alpha MEM is an aqueous composition having the following components:

Component: Inorganic Salts	mg/L
CaCl ₂ (anhyd.)	200.00
CaCl ₂ •2H ₂ O	--
KCl	400.00
MgSO ₄ (anhyd.)	97.67
MgSO ₄ •7H ₂ O	--
NaCl	6800.00
NaHCO ₃	2200.00
NaH ₂ PO ₄ •H ₂ O	140.00
NaH ₂ PO ₄ •2H ₂ O	--
Other Components:	mg/L
D-Glucose	1000.00
Lipoic Acid	0.20
Phenol Red	10.00

- 172 -

Sodium Pyruvate	110.00
Amino Acids:	mg/L
L-Alanine	25.00
L-Arginine•HCl	126.00
L-Asparagine•H ₂ O	50.00
L-Aspartic Acid	30.00
L-Cystine	--
L-Cystine•2HCl	31.00
L-Cysteine HCl	--
L-Cysteine HCl•H ₂ O	100.00
L-Glutamic Acid	75.00
L-Glutamine	292.00
L-Alanyl-L-Glutamine	--
Glycine	50.00
L-Histidine HCl•H ₂ O	42.00
L-Isoleucine	52.00
L-Leucine	52.00
L-Lysine•HCl	73.00
L-Methionine	15.00
L-Phenylalanine	32.00
L-Proline	40.00
L-Serine	25.00
L-Threonine	48.00
L-Tryptophan	10.00
L-Tyrosine	--
L-Tyrosine (disodium salt)	52.00

- 173 -

L-Valine	46.00
Vitamins:	mg/L
L-Ascorbic acid	50.00
Biotin	0.10
D-Ca Pantothenate	1.00
Choline Chloride	1.00
Folic acid	1.00
i-Inositol	2.00
Niacinamide	1.00
Pyridoxal HCl	1.00
Riboflavin	0.10
Thiamine HCl	1.00
Vitamin B ₁₂	1.40
Ribonucleosides	mg/L
Adenosine	10.00
Cytidine	10.00
Guanosine	10.00
Uridine	10.00
Deoxyribonucleosides	mg/L
2' Deoxyadenosine	10.00
2' Deoxycytidine HCl	11.00
2' Deoxyguanosine	10.00
Thymidine	10.00

The instant compounds, which are useful for treating the above discussed disease states, will preferably have IC₅₀ values at one, two or all of the PPAR (PPAR γ , PPAR δ or PPAR α) receptor cites of

- 174 -

equal to or less than 10 μ M binding assay, and an EC₅₀ equal to or less than 10 μ M in the transactivation assay. Preferably, an IC₅₀ of 100 nM in the binding assay, and an EC₅₀ equal to or less than 100 nM in the transactivation assay. More preferably, the instant compounds have an IC₅₀ equal to or less than 50 nM in the binding assay, and an EC₅₀ equal to or less than 50 nM in the transactivation assay. Most preferably, the instant compounds have an IC₅₀ equal to or less than 10 nM in the binding assay, and an EC₅₀ equal to or less than 10 nM in the transactivation assay..

PPAR Receptor Binding Assay

A. Preparation of Human PPAR γ 2 and δ

Human PPAR γ 2 and PPAR δ , independently, were prepared as gst-fusion proteins in *E. coli*. The full length human cDNA for PPAR γ 2 and PPAR δ were subcloned into the PGEX-2T and PGEX-KT, respectively, expression vector (Pharmacia). *E. coli* containing the plasmid were grown, induced, and then harvested by centrifugation. The resuspended pellet was broken in a French press and debris was removed by centrifugation at 12,000Xg. Receptors were purified from the supernatant by affinity chromatography on glutathione sepharose. After application to the column, and 1 wash, receptor was eluted with glutathione. Glycerol was added to stabilize the receptor and aliquots were frozen at -80 °C for later use.

B. [³H]AD-5075 and Example 11 Displacement Assay for PPAR γ 2 and PPAR δ , respectively

For each assay, an aliquot of receptor (1:1000-1:3000 dilution) was incubated in TEGM (10 mM Tris, pH 7.2, 1 mM EDTA, 10% glycerol, 7 μ l/100 ml β -mercaptoethanol, 10 mM Na molybdate, 1 mM dithiothreitol, 5 μ g/ml aprotinin, 2 μ g/ml leupeptin, 2 μ g/ml benzamide and 0.5 mM PMSF) containing 5-10% COS-1 cell cytoplasmic lysate and 10 nM labeled thiazolidinedione ([³H₂]AD-5075, 21 Ci/mmole), \pm test compound compound, [³H₂]Example 11, 17 Ci/mmole), \pm test compound, respectively. Assays were incubated for

- 175 -

~16 h at 4 °C in a final volume of 300 µl. Unbound ligand was removed by addition of 200 µl dextran/gelatin-coated charcoal, on ice, for ~10 minutes. After centrifugation at 3000 rpm for 10 min at 4 °C, 200 µl of the supernatant fraction was counted in a liquid scintillation counter. In this assay the K_D for AD-5075 and Example 11 is 1 nM, respectively.

PPAR Receptor Transactivation Assay

A. Activation of hPPAR γ and hPPAR δ Methods

1. Plasmids

The chimeric receptor expression constructs, pSG5-hPPAR γ 2/GR and pSG5-hPPAR δ /GR, were prepared by inserting the DNA binding domain of the murine glucocorticoid receptor adjacent to the ligand binding domain of hPPAR γ 2 or hPPAR δ . These vectors were kindly provided by Dr. Azriel Schmidt (MRL). The glucocorticoid receptor -responsive reporter vector, pMMTV/luc/neo, contains the murine mammary tumour virus (MMTV) promoter adjacent to the luciferase gene (luc) and the neomycin resistance gene (neo). It was constructed from pMMTV/luc which was provided by Dr. Azriel Schmidt (Merck Research Laboratories). Prior to transfection into CHO-K1 cells, pSG5-hPPAR γ 2/GR and pSG5-hPPAR δ /GR were linearized with Xba I. pMMTV/luc/neo DNA was cut with Pvu I. Wild type receptor constructs, pSG5-hPPAR γ 2, pSG5-hPPAR δ and pSG5-hPPAR α were prepared by inserting the full-length hPPAR γ 2, hPPAR δ and PPAR α cDNAs adjacent to the SV40 promoter in pSG5. The PPAR-responsive reporter construct, pPPRE-luc, contained 3 copies of a generic PPRE placed adjacent to the thymidine kinase minimal promoter and the luciferase reporter gene. The transfection control vector, pCMV-lacZ, contains the galactosidase Z gene under the regulation of the cytomegalovirus promoter.

2. Production of stable cell lines

CHO-K1 cells were seeded overnight at 6×10^5 cells /60 mm dish in alpha Minimum Essential Medium (MEM) containing 10% fetal calf serum (FCS), 10 mM HEPES, 100 units/ml PenicillinG and 100

- 176 -

$\mu\text{g/ml}$ Streptomycin sulfate at 37°C in an atmosphere of 10% CO_2 in air. The cells were washed once with OptiMEM 1 Reduced-Serum Medium and then cotransfected with 4.5 μg of pSG5-hPPAR γ 2 /GR or pSG5-hPPAR δ /GR expression vector and 0.5 μg of pMMTV/luc/neo in the presence of 100 μg Lipofectamine (GIBCO BRL) according to the instructions of the manufacturer. Transfection medium was removed 2 h later and replaced with growth medium. After being incubated for 3 days, cells were subcultured by diluting the cell suspension 1/1250 and 1/6250 and placing the cells in a 100 mm culture dish. Selection of the stable cell lines was initiated the next day by adding 500 $\mu\text{g/ml}$ G418 to the medium. Cells were routinely fed with the selection media for 1 month at which time 120 colonies were picked and transferred to 24 well culture plates. Ten days later, confluent colonies were transferred to 6 well plates to maintain stocks and to 96 well plates to assay for luciferase activity. Positive clones were characterized and validated by titrating 4 known agonists on each clone. Two clones, g2B2P2D9 and d2A5P2G3, were selected for screening purposes.

B. hPPAR/GR transactivation screens in stably transfected CHO-K1 cells

The hPPAR γ 2/GR and hPPAR δ /GR stable CHO-K1 cell lines were seeded at 1×10^4 cells/well in 96 well cell culture plates in alpha MEM containing 10% FCS, 10 mM HEPES, and 500 mg/ml G418 at 37°C in an atmosphere of 10% CO_2 in air. After a 20 hour incubation, cells were washed once with alpha MEM and then incubated in an atmosphere of 10% CO_2 in air in alpha MEM containing 5% charcoal stripped FCS, 10 mM HEPES, and 500 mg/ml G418. The cells were incubated for 24 hours in the absence of test compound or in the presence of a range of concentrations of test compound. Cell lysates were prepared from washed cells using Reporter Lysis Buffer (Promega) according to the manufacturer's directions. Luciferase activity in cell extracts was determined using Luciferase Assay Reagent buffer (Promega) in a ML3000 luminometer (Dynatech Laboratories).

Transactivation Wild-Type Assay

A. Characterization of ligand activity on wild-type hPPAR γ , hPPAR δ and hPPAR α .

COS-1 cells were seeded at 0.5×10^5 cells/dish into 24 well plates in Dulbecco's modified Eagle medium (high glucose) containing 10% charcoal stripped fetal calf serum, nonessential amino acids, 100 units/ml Penicillin G and 100 μ g/ml Streptomycin sulfate at 37°C in a humidified atmosphere of 10% CO₂. After 24 hours, transfections were performed with Lipofectamine (Gibco-BRL, Gaithersburg, MD) according to the instructions of the manufacturer. In general, for transactivation experiments, transfection mixes contained 0.15 mg of hPPAR γ 2 hPPAR α or hPPAR δ expression vector, 0.15 mg of reporter vector pPPRE-luc and 0.001 mg of pCMV-lacZ as an internal control of transfection efficiency. Compounds demonstrating significant agonist activity in the above primary screen were further characterized by incubation with transfected cells for 48h across a range of concentrations. Luciferase activity was determined as described above.

In a similar manner, hPPAR γ 1 cDNA can be used in place of hPPAR γ 2 cDNA in the methods described in Example 5 to make the wild type receptor construct, pSG5-hPPAR γ 1.

III. In Vivo Studies

Methods

db/db Mice are obese, highly insulin resistant animals. The db locus has been shown to code for the leptin receptor. These animals are substantially hypertriglyceridemic and hyperglycemic.

Male db/db mice (10-11 week old C57Bl/KFJ, Jackson Labs, Bar Harbor, ME) were housed 5/cage and allowed *ad lib.* access to ground Purina rodent chow and water. The animals, and their food, were weighed every 2 days and were dosed daily by gavage with vehicle (0.5% carboxymethylcellulose) \pm test compound at the indicated dose. Drug suspensions were prepared daily. Plasma glucose, Cholesterol and triglyceride concentrations were determined from blood obtained by tail

- 178 -

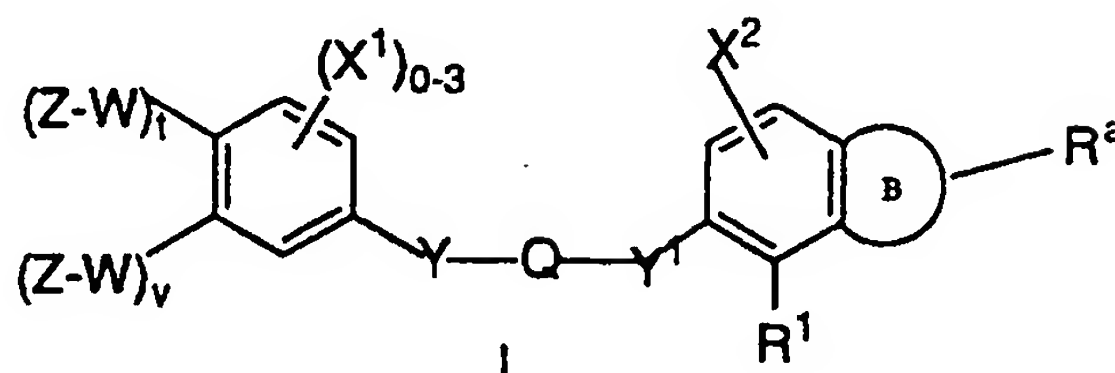
bleeds at 3-5 day intervals during the study period. Glucose, cholesterol and triglyceride, determinations were performed on a Boehringer Mannheim Hitachi 911 automatic analyzer (Boehringer Mannheim, Indianapolis, IN) using heparinized plasma diluted 1:5, or 1:6 (v/v) with normal saline. Lean animals were age-matched heterozygous mice maintained in the same manner. The instant compounds were found to lower triglyceride and glucose levels at a dose of about 100mg/kg, preferably a dose of about 10-50 mg/kg, when administered by oral gavage daily for a period of at least 5 days.

Lipoprotein analysis was performed on either serum, or EDTA treated plasma obtained by heart puncture from anesthetized animals at the end of the study. Apolipoprotein concentrations were determined by ELISA, and cholesterol particles were analyzed by FPLC, precipitation, or ultracentrifugation. Total liver RNA was prepared from tissue that had been frozen on liquid nitrogen at the time of euthanasia. Apolipoprotein mRNA was analyzed on Northern Blots using specific probes for mouse or rat proteins.

- 179 -

WHAT IS CLAIMED IS:

1. A compound having the formula I:



or a pharmaceutically acceptable salt thereof, wherein:

R is selected from the group consisting of H, C₁-6 alkyl, C₅-10 aryl, and C₅-10 heteroaryl, said alkyl, aryl and heteroaryl optionally substituted with 1 to 3 groups of R^a;

R¹ is selected from a group consisting of: H, C₁-15 alkyl, C₂-15 alkenyl, C₂-15 alkynyl and C₃-10 cycloalkyl, said alkyl, alkenyl, alkynyl, and cycloalkyl optionally substituted with 1 to 3 groups of R^a;

R³ is selected from a group consisting of: H, NHR¹, NHacyl, C₁-15 alkyl, C₃-10 cycloalkyl, C₂-15 alkenyl, C₁-15 alkoxy, CO₂alkyl, OH, C₂-15 alkynyl, C₅-10 aryl, C₅-10 heteroaryl said alkyl, cycloalkyl, alkenyl, alkynyl, aryl and heteroaryl optionally substituted with 1 to 3 groups of R^a;

(Z-W-) is Z-CR⁶R⁷-, Z-CH=CH-, or $Z-\overset{\overset{R^6}{\diagup}}{\underset{\diagdown}{C}}-R^8-$;

R⁸ is selected from the group consisting of CR⁶R⁷, O, NR⁶, and S(O)_p;

R⁶ and R⁷ are independently selected from the group consisting of H, C₁₋₆ alkyl;

- 180 -

B is a 5 or 6 membered heterocycle containing 0 to 2 double bonds, and 2 heteroatoms independently selected from the group consisting of O, N and S, said heteroatoms are optionally substituted at any position on the five or six membered heterocycle, the heterocycle being optionally unsubstituted or substituted with 1 to 3 groups of R^a ;

X^1 and X^2 are independently selected from a group consisting of: H, OH, C₁₋₁₅ alkyl, C₂₋₁₅ alkenyl, C₂₋₁₅ alkynyl, halo, OR^3 , $ORCF_3$, C₅₋₁₀ aryl, C₅₋₁₀ aralkyl, C₅₋₁₀ heteroaryl and C₁₋₁₀ acyl, said alkyl, alkenyl, alkynyl, aryl and heteroaryl optionally substituted with 1 to 3 groups of R^a ;

R^a represents a member selected from the group consisting of: halo, acyl, aryl, heteroaryl, CF_3 , OCF_3 , CN, NO_2 , R^3 , OR^3 , SR^3 , $S(O)R^3$, $=N(OR)$, SO_2R^3 , NR^3R^3 , NR^3COR^3 , $NR^3CO_2R^3$, $NR^3CON(R^3)_2$, $NR^3SO_2R^3$, COR^3 , CO_2R^3 , $CON(R^3)_2$, $SO_2N(R^3)_2$, $OCON(R^3)_2$ said aryl and heteroaryl optionally substituted with 1 to 3 groups of halo or C₁₋₆ alkyl;

Y is selected from the group consisting of: $S(O)_p$, $-CH_2-$, $-C(O)-$, $-C(O)NH-$, $-NR-$, $-O-$, $-SO_2NH$, $-NH SO_2$;

Y^1 is selected from the group consisting of: O and C;

Z is selected from the group consisting of: CO_2R^3 , $CONHSO_2R$, $CONH_2$ and 5-(1H-tetrazole);

t and v are independently 0 or 1 such that $t + v = 1$;

Q is a saturated or unsaturated straight chain hydrocarbon containing 2-4 carbon atoms and

p is 0-2.

- 181 -

2. A compound of Claim 1 where X^1 & X^2 are independently H or halo.
3. A compound of Claim 1 where Y is O.
4. A compound of Claim 1 where Y is $S(O)_p$, wherein p is 0-2.
5. A compound of Claim 1 where Y is $-CH_2-$.
6. A compound of Claim 1 where Y is $-CO-$.
7. A compound of Claim 1 where Y is $-NH-$.
8. A compound of Claim 1 where Y is $-NHSO_2$ or $-SO_2NH$.
9. A compound of Claim 1 where Y is $-C(O)NH-$.
10. A compound of Claim 1 where (Z-W-) is $Z-CR^6R^7-$
or $Z-\overset{\overset{R^6}{\diagup}}{\underset{\diagdown}{C}}-R^8-$;
11. A compound of Claim 1 where B is a 5 or 6 membered heterocycle containing 0 to 2 double bonds, and 2 heteroatoms independently selected from the group consisting of O, N and S, said heteroatoms are optionally substituted at any position on the five or six membered heterocycle, the heterocycle being optionally unsubstituted or substituted with 1 to 3 groups of R^a .
12. A compound of Claim 1 wherein:

- 182 -

R is C₁-6 alkyl or C₅-10 aryl, said alkyl or aryl optionally substituted with 1 to 3 groups of R^a

R¹ is C₁-15 alkyl;

X¹ & X² are independently H, C₁-6 alkyl or halo;

Y is O, NH or S;

Y¹ is O;

(Z-W-) is Z-CR⁶R⁷- or $\begin{array}{c} \text{R}^6 \quad \text{R}^7 \\ \diagdown \quad / \\ \text{Z}-\text{C}-\text{R}^8- \end{array}$;

R^a is a member selected from the group consisting of: halo, acyl, aryl, heteroaryl, CF₃, OCF₃, CN, NO₂, R³, OR³, SR³, S(O)R³, SO₂R³, NR³COR³, COR³, CON(R³)₂, SO₂N(R³)₂, said aryl and heteroaryl optionally substituted with 1 to 3 groups of halo or C₁-6 alkyl; and

Z is CO₂R³, CONHSO₂R, CONH₂ or 5-(1H-tetrazole).

13. A compound of Claim 1 selected from the group consisting of:

Methyl 3-chloro-4-(3-(3-ethyl-7-propyl-6-benz-[4,5]-isoxazoloxy)-propylthio)phenylacetate;

3-chloro-4-(3-(3-ethyl-7-propyl-6-benz-[4,5]-isoxazoloxy)propylthio)-phenylacetic acid;

Methyl 3-chloro-4-(3-(3-methoxy-7-propyl-6-benz-[4,5]-isoxazoloxy)-propylthio)phenylacetate;

3-chloro-4-(3-(3-methoxy-7-propyl-6-benz-[4,5]-isoxazoloxy)propylthio)-phenylacetic acid;

- 183 -

Methyl 3-chloro-4-(3-(3-ethyl-7-propyl-6-benz-[4,5]-isothiazoloxy)-propylthio)phenyl acetate;

3-chloro-4-(3-(3-ethyl-7-propyl-6-benz-[4,5]-isothiazole)oxy)propylthio phenylacetic acid;

Methyl 3-chloro-4-(3-(3-methyl-7-propyl-6-benz-[4,5]-isoxazoloxy)-propylthio)phenylacetate;

3-chloro-4-(3-(3-methyl-7-propyl-6-benz-[4,5]-isoxazoloxy)propylthio)-phenylacetic acid;

Methyl 3-chloro-4-(3-(3,7-dipropyl-6-benz-[4,5]-isoxazoloxy)propylthio)-phenylacetate;

3-chloro-4-(3-(3,7-dipropyl-6-benz-[4,5]-isoxazoloxy)propylthio) phenyl-acetic acid;

Methyl 3-chloro-4-(3-(3-ethyl-7-propyl-6-benz-[4,5]-isoxazoloxy)-propylthio)phenylacetate S-oxide;

3-chloro-4-(3-(3-ethyl-7-propyl-6-benz-[4,5]-isoxazoloxy)propylthio)-phenylacetic acid S-oxide;

Methyl 3-chloro-4-(3-(3-ethyl-7-propyl-6-benz-[4,5]-isoxazoloxy)propyl-thio)phenylacetate S,S-dioxide;

3-Chloro-4-(3-(3-ethyl-7-propyl-6-benz-[4,5]-isoxazole)oxy)-propylthio phenylacetic acid S,S-dioxide;

tert-Butyl 3-chloro-4-(3-(3-ethyl-7-propyl-6-benz-[4,5]-isoxazoloxy)-propylthio)phenyl acetate;

- 184 -

2-methyl-2-(3-chloro-4-(3-(3-phenyl-7-propylbenz[4,5]isoxazol-6-oxy)propyl)thio)phenyl propionic acid;

Methyl 3-chloro-4-(3-(3-(2,2-dimethylpropyl)-7-propyl-6-benz-[4,5]-isoxazoloxy)-propylamino)phenylacetate;

3-Chloro-4-(3-(3-(2,2-dimethylpropyl)-7-propyl-6-benz-[4,5]-isoxazoloxy)-propylamino)phenylacetic acid;

3-Chloro-4-(3-(2-phenyl-6-propyl-5-benz-[4,7]-oxazoloxy)propylthio)phenylacetic acid;

Methyl 3-propyl-4-(3-(3-trifluoromethyl-7-propyl-6-benz-[4,5]-isoxazoloxy)-propylthio)phenylacetate;

3-propyl-4-(3-(3-trifluoromethyl-7-propyl-6-benz-[4,5]-isoxazoloxy)-propylthio)phenylacetic acid;

3-chloro-4-(3-(2-propyl-3-trifluoromethyl-6-benz-[4,5]-isoxazoloxy)propylthio)phenylacetic acid;

3-chloro-4-(3-(3-phenyl-7-cyclopropylmethyl-6-benz-[4,5]-isoxazoloxy)-butyloxy)phenylacetic acid;

4-(3-(3-Phenyl-7-propylbenzisoxazol-6-yloxy)propylthio)-phenyl(2,2-dimethyl)acetic acid;

3-(3-(3-Phenyl-7-propylbenz[c]pyrazol-6-yloxy)propylamino)-phenyl(2,2-dimethyl)acetic acid;

4-(3-(3-Phenyl-7-propylbenz[c]pyrazol-6-yloxy)propylamino)-phenyl(2,2-dimethyl)acetic acid;

- 185 -

4-(3-(3-Phenyl-7-propylbenzoxazol-6-yloxy)propyloxy)-phenylpropan-3-oic acid;

4-(4-(3-Phenyl-7-propylbenz[c]pyrazol-6-yloxy)butylamino)-phenylpropan-3-oic acid;

3-(3-(3-Phenyl-7-propylbenzoxazol-6-yloxy)propylthio)-phenoxyacetic acid;

4-(3-(3-Phenyl-7-propylbenzoxazol-6-yloxy)propylthio)-phenoxyacetic acid;

4-(4-(1-Phenyl-4-propylbenz[d]triazol-5-yloxy)butyloxy)-phenoxyacetic acid;

N-[4-(3-(3-Phenyl-7-propylbenzoxazol-6-yloxy)propylamino)-phenyl]glycine;

N-[3-(4-(4-Phenyl-8-propylquinazolin-7-yloxy)butyloxy)-phenyl]glycine;

N-[4-(4-(4-Phenyl-8-propylquinazolin-7-yloxy)butyloxy)-phenyl]glycine;

4-(3-(3-Phenyl-7-propylbenzoxazol-6-yloxy)propylamino)-phenylacetic acid;

4-(3-(4-Phenyl-8-propylquinazolin-7-yloxy)propylthio)-phenylacetic acid;

3-(3-(2-Phenyl-6-propylbenzoxazol-5-yloxy)propylamino)-3-chlorophenylacetic acid;

- 186 -

4-(3-(2-Phenyl-6-propylbenzoxazol-5-yloxy)propylamino)-3-chlorophenylacetic acid;

4-(3-(2-Phenyl-6-propylbenzoxazol-5-yloxy)propylamino)-phenylacetic acid;

3-(3-(2-Phenyl-5-propylbenzisoxazol-6-yloxy)propylamino)-3-chlorophenylacetic acid;

4-(3-(1-Phenyl-4-propylbenz[d]triazol-5-yloxy)propylamino)-3-chlorophenylacetic acid;

3-(3-(3-Phenyl-7-propylbenz[c]pyrazol-6-yloxy)propylamino)-3-chlorophenylacetic acid;

4-(3-(3-Phenyl-7-propylbenzisoxazol-6-yloxy)propylamino)-3-chlorophenylacetic acid;

4-(4-(3-Phenyl-7-prop-2-enylbenzisoxazol-6-yloxy)butyloxy)-3-chlorophenylacetic acid;

4-(3-(3-Phenyl-7-propylbenzisoxazol-6-yloxy)propylamino)-phenoxyacetic acid;

3-(3-(3-Phenyl-7-butylbenzisoxazol-6-yloxy)propylthio)-phenylpropan-3-oic acid;

4-(3-(3-Phenyl-7-butylbenzisoxazol-6-yloxy)propylthio)-phenylpropan-3-oic acid;

4-(3-(3-Phenyl-7-propylbenzisoxazol-6-yloxy)propyloxy)-2-phenyl-2,2-dimethylacetic acid;

- 187 -

4-(4-(3-Phenyl-7-(cyclopropylmethyl)benzisoaxazol-6-yloxy)butylamino)-phenoxy-2,2-dimethylacetic acid;

3-(3-(3-Neopentyl-7-propylbenzisoaxazol-6-yloxy)propylthio)-3-methylphenylacetic acid

4-(3-(3-(2-Phenyl-2,2-dimethyl)-7-propylbenzisoaxazol-6-yloxy)propyloxy)-3-butylphenylacetic acid;

4-(3-(3-Chloro-7-propylbenzisoaxazol-6-yloxy)propylamino)-2-propylphenylacetic acid;

3-(3-(3-Chloro-7-propylbenzisoaxazol-6-yloxy)propylamino)-2-propylphenylacetic acid;

4-(4-(3-Butoxy-7-propylbenzisoaxazol-6-yloxy)butylthio)-2-fluorophenylacetic acid;

4-(3-(3-Phenyl-7-propylbenzisoaxazol-6-yloxy)propylamino)-phenoxyacetic acid;

3-(3-(3-(3-Butylphenyl)-7-butylbenzisoaxazol-6-yloxy)propylthio)-phenylpropan-3-oic acid;

4-(3-(3-(2-Tolyl)-7-butylbenzisoaxazol-6-yloxy)propylthio)-phenylpropan-3-oic acid;

4-(3-(3-(4-Fluorophenyl)-7-propylbenzisoaxazol-6-yloxy)propyloxy)-2-phenyl-2,2-dimethylacetic acid;

4-(3-(3-Phenyl-7-propylbenzisoaxazol-6-yloxy)propyloxy)-phenoxy-2-*spiro*-cyclopropylacetic acid;

- 188 -

3-(3-(3-Phenyl-7-propylbenzisoxazol-6-yloxy)propyloxy)-phenoxy-2-
spiro-cyclopropylacetic acid;

5-(4-(3-(3-Phenyl-7-propylbenz[c]pyrazol-6-yloxy)propylamino)phenyl-
2-(2,2-dimethyl)-ethyl)-tetrazole;

5-(4-(3-(3-Phenyl-7-propylbenzisoxazol-6-yloxy)propyloxy)phenyl-3-
propyl)-tetrazole;

5-(4-(4-(1-Phenyl-4-propylbenz[d]triazol-5-yloxy)butylamino)phenyl-3-
propyl)-tetrazole;

5-(3-(3-(3-Phenyl-7-propylbenzisoxazol-6-yloxy)propylthio)phenoxy-2-
ethyl)-tetrazole;

5-(4-(3-(3-Phenyl-7-propylbenzisoxazol-6-yloxy)propylthio)phenoxy-2-
ethyl)-tetrazole;

3-chloro-4-(3-(3-ethyl-7-propyl-6-benz-[4,5]-isoxazoloxy)-but-2-en-
thio)phenylacetic acid;

4-(3-(3-ethyl-7-propyl-6-benz[4,5]isoxazole)oxy)propyloxy phenoxy
acetic acid;

N-Methylsulfonyl 3-chloro-4-(3-(3-ethyl-7-propyl-6-benz[4,5]
isoxazole)oxy)propylthio phenyl acetamide;

3,5-dimethoxy-4-(3-(3-(Ethyl)-7-(propyl)-6-benz-[4,5]-isoxazoloxy)-
propyloxy)phenyl acetic acid;

3,5-dichloro-4-(3-(3-(Ethyl)-7-(propyl)-6-benz-[4,5]-isoxazoloxy)-
propyloxy)phenyl acetic acid;

3,5-dimethyl-4-(3-(3-(Ethyl)-7-(propyl)-6-benz-[4,5]-isoxazoloxy)-
propyloxy)phenyl acetic acid;

- 189 -

4-(3-(3-(Ethyl)-7-(propyl)-6-benz-[4,5]-isoxazoloxy)-propyloxy)-phenyl propionic acid;

3-chloro-4-(3-phenylmethyl-7-(n-propyl)-6-benz[4,5]isoxazoloxy)propyl-thio)phenylacetic acid;

3-chloro-4-(3-(2,2-dimethylpropyl)-7-(n-propyl)-6-benz[4,5]isoxazoloxy)-propylthio)phenylacetic acid;

2-methyl-4-(3-(3-(Ethyl)-7-(propyl)-6-benz-[4,5]-isoxazoloxy)propyloxy)-phenyl propionic acid;

3-Propyl-4-(3-(3-ethyl-7-propyl-6-benz-[4,5]-isoxazoloxy)-propyloxy)phenylacetic acid;

4-(3-(3-(Ethyl)-7-propyl-6-benz-[4,5]-isoxazoloxy)butyl)phenylacetate;

3-chloro-4-(7-(n-propyl)-3-(3,3,3-trifluoropropyl)-6-benz[4,5]isoxazoloxy)propylthio)phenylacetic acid;

3-chloro-4-(3-(4-chlorophenylmethyl)-7-(n-propyl)-6-benz[4,5]isoxazol-oxy)propylthio)phenylacetic acid;

3-Chloro-4-(3-(3-(2,2-dimethylpropyl)-7-propyl-6-benz-[4,5]-isoxazoloxy)propyl- N-methylamino)phenylacetate;

3,5-Dipropyl-4-(3-(3-ethyl-7-propyl-6-benz-[4,5]-isoxazoloxy)-propyloxy)phenylacetic acid;

3-fluoro-4-(3-(7-propyl-3-trifluoromethyl-6-benz-[4, 5]isoxazoloxy)-propyloxy)phenylacetic acid;

- 190 -

3-chloro-4-(3-(3-trifluoromethyl-7-propyl-6-benz-[4, 5]-isoxazoloxy)propylamino)phenylacetic acid;

3-Isobutyl-4-(3-(3-neo-pental-7-propyl-6-benz-[4,5]-isoxazoloxy)-propyloxy)phenylacetic acid;

3-Propyl-4-(3-(3-neo-pental-7-propyl-6-benz-[4,5]-isoxazoloxy)propylthio)phenylacetic acid S,S-dioxide;

-Chloro-4-(3-(3-phenyl-7-propyl-6-benz-[4,5]-isoxazoloxy)-propylsulfoxy)phenylacetic acid;

3-fluoro-4-(4-(3-phenyl-7-propyl-6-benz-[4, 5]-isoxazoloxy)-butyloxy)phenylacetic acid;

3-chloro-4-(3-(7-propyl-3-trifluoromethyl-6-benz-[4, 5]-isoxazoloxy)-propyl-thio)phenylacetic acid S, S-dioxide;

3-chloro-4-(3-(7-propyl-3-trifluoromethyl-6-benz-[4, 5]-isoxazoloxy)-propyl-thio)phenylacetic acid S-oxide;

3-chloro-4-(3-(2-phenylethyl)-7-propyl-6-benz[4,5]isoxazoloxy)propyl-thio)phenylacetic acid;

3-Chloro-4-(3-(3-(4-fluorophenyl)-7-propyl-6-benz-[4,5]-isoxazoloxy)-propylthio)phenylacetic acid;

3-Chloro-4-(3-(3-(4-fluorophenyl)-7-propyl-6-benz-[4,5]-isoxazoloxy)-propylsulfinyl)phenylacetic acid;

3-Chloro-4-(3-(3-(4-fluorophenyl)-7-propyl-6-benz-[4,5]-isoxazoloxy)-propylsulfonyl) phenylacetic acid;

2,3-Dichloro-4-(3-(3-neo-pental-7-propyl-6-benz-[4,5]-isoxazoloxy)-propylthio)phenylacetic acid;

- 191 -

2-Trifluoroethoxy-4-(3-(3-neo-pental-7-propyl-6-benz-[4,5]-isoxazoloxy)propyloxy)phenylacetic acid;

3-Chloro-4-(3-(3-cyclopropyl)-7-propyl-6-benz-[4,5]-isoxazoloxy)-propylamino)phenylacetate;

2-(3-chloro-4-(3-(3-ethyl-7-propyl-6-benz-[4,5]-isoxazoloxy)propylthio)) phenylpropionic acid;

3-(4-(3-(3-phenyl-7-propyl-6-benz-[4,5]-isoxazoloxy)propyloxy)) phenylpropionic acid;

3-Chloro-4-(3-(3-(3-fluorophenyl)-7-propyl-6-benz-[4,5]-isoxazoloxy)-propylthio)phenylacetic acid;

3-Chloro-4-(3-(3-neo-pental-7-propyl-6-benz-[4,5]-isoxazoloxy)-propyloxy)phenoxylacetic acid;

4-(3-(3-phenyl-7-propyl-6-benz[4,5]isoxazole)oxy)propyloxy phenoxy acetic acid;

(3-(4-(3-phenyl-7-propyl-6-benz-[4,5]-isoxazoloxy)butyloxy)) phenylacetic acid;

3-(4-(4-(3-phenyl-7-propyl-6-benz-[4,5]-isoxazoloxy)butyloxy)) phenylpropionic acid;

3-chloro-4-(3-(2-methyl-2-phenylpropyl)-7-(n-propyl)-6-benz[4,5]isoxazoloxy)propylthio)phenylacetic acid;

3-Methoxy-4-(3-(3-(2,2-dimethylpropyl)-7-propyl-6-benz-[4,5]-isoxazoloxy)propyloxy)phenylacetate;

3-(4-(2-(3-phenyl-7-propyl-6-benz-[4,5]-isoxazoloxy)ethyloxy)) phenylpropionic acid;

- 192 -

(3-(4-(3-phenyl-7-propyl-6-benz-[4,5]-isoxazoloxy)butyloxy))
phenoxyacetic acid;

E-(4-(3-(3-phenyl-7-propyl-6-benz[4,5]isoxazole)oxy)propyloxy)
cinnamic acid;

E-(3-(3-(3-phenyl-7-propyl-6-benz[4,5]isoxazole)oxy)propyloxy)
cinnamic acid;

3-(3-(3-(3-phenyl-7-propyl-6-benz[4,5]isoxazole)oxy)propyloxy)
phenylpropionic acid;

N-((4-carbomethoxymethyl)benzoyl)-3(3-phenyl-7-propyl-6-benz-[4,7]-
isooxazolyloxy) propylamine ;

2-(4-(3-(3-phenyl-7-propyl-6-benz-[4,5]-isoxazoloxy)propyloxy))
phenoxypropionic acid;

2-(4-(4-(3-phenyl-7-propyl-6-benz-[4,5]-isoxazoloxy)butyloxy))
phenoxypropionic acid;

3-chloro-4-(3-(7-cyclopropylmethyl-3-phenyl-6-benz-[4, 5]-
isoxazoloxy)propyl-thio)phenylacetic acid;

1-(3-chloro-4-(3-(3-(2,2-dimethylpropyl)-7-propyl-6-
benz[4,5]isoxazole)oxy)propylthio) phenyl cyclopropane carboxylic
acid;

4-(3-(3-(Ethyl)-7-(phenyl)-6-benz-[4,5]-isoxazoloxy)propyloxy)-3-
chloro- α , α -dimethyl-phenyl propionic acid;

3-Ethoxy-4-(3-(3-(2,2-dimethylpropyl)-7-propyl-6-benz-[4,5]-
isoxazoloxy)propyloxy)phenylacetate; and

3-chloro-4-(3-(3-phenyl-6-propyl-5-benz-[4,7]-isoxazolyloxy)-
propylthio) phenylacetic acid.

- 193 -

14. A compound of Claim 12 selected from the group consisting of:

Methyl 3-chloro-4-(3-(3-ethyl-7-propyl-6-benz-[4,5]-isoxazoloxy)-propylthio)phenylacetate;

3-chloro-4-(3-(3-ethyl-7-propyl-6-benz-[4,5]-isoxazoloxy)propylthio)-phenylacetic acid;

Methyl 3-chloro-4-(3-(3-methoxy-7-propyl-6-benz-[4,5]-isoxazoloxy)-propylthio)phenylacetate;

3-chloro-4-(3-(3-methoxy-7-propyl-6-benz-[4,5]-isoxazoloxy)propylthio)-phenylacetic acid;

Methyl 3-chloro-4-(3-(3-ethyl-7-propyl-6-benz-[4,5]-isothiazoloxy)-propylthio)phenyl acetate;

3-chloro-4-(3-(3-ethyl-7-propyl-6-benz-[4,5]-isothiazole)oxy)propylthio phenylacetic acid;

Methyl 3-chloro-4-(3-(3-methyl-7-propyl-6-benz-[4,5]-isoxazoloxy)-propylthio)phenylacetate;

3-chloro-4-(3-(3-methyl-7-propyl-6-benz-[4,5]-isoxazoloxy)propylthio)-phenylacetic acid;

Methyl 3-chloro-4-(3-(3,7-dipropyl-6-benz-[4,5]-isoxazoloxy)propylthio)-phenylacetate;

3-chloro-4-(3-(3,7-dipropyl-6-benz-[4,5]-isoxazoloxy)propylthio) phenyl-acetic acid;

Methyl 3-chloro-4-(3-(3-ethyl-7-propyl-6-benz-[4,5]-isoxazoloxy)-propylthio)phenylacetate S-oxide;

- 194 -

3-chloro-4-(3-(3-ethyl-7-propyl-6-benz-[4,5]-isoxazoloxy)propylthio)-phenylacetic acid S-oxide;

Methyl 3-chloro-4-(3-(3-ethyl-7-propyl-6-benz-[4,5]-isoxazoloxy)propyl-thio)phenylacetate S,S-dioxide;

3-Chloro-4-(3-(3-ethyl-7-propyl-6-benz-[4,5]-isoxazole)oxy)-propylthio phenylacetic acid S,S-dioxide;

tert-Butyl 3-chloro-4-(3-(3-ethyl-7-propyl-6-benz-[4,5]-isoxazoloxy)-propylthio)phenyl acetate;

2-methyl-2-(3-chloro-4-(3-(3-phenyl-7-propylbenz[4,5]isoxazol-6-oxy)propyl)thio)phenyl propionic acid;

Methyl 3-chloro-4-(3-(3-(2,2-dimethylpropyl)-7-propyl-6-benz-[4,5]-isoxazoloxy)-propylamino)phenylacetate;

3-Chloro-4-(3-(3-(2,2-dimethylpropyl)-7-propyl-6-benz-[4,5]-isoxazoloxy)-propylamino)phenylacetic acid;

3-Chloro-4-(3-(2-phenyl-6-propyl-5-benz-[4,7]-oxazoloxy)propylthio)phenylacetic acid;

Methyl 3-propyl-4-(3-(3-trifluoromethyl-7-propyl-6-benz-[4,5]-isoxazoloxy)-propylthio)phenylacetate;

3-propyl-4-(3-(3-trifluoromethyl-7-propyl-6-benz-[4,5]-isoxazoloxy)-propylthio)phenylacetic acid;

3-chloro-4-(3-(2-propyl-3-trifluoromethyl-6-benz-[4,5]-isoxazoloxy)propylthio)phenylacetic acid;

- 195 -

3-chloro-4-(3-(3-phenyl-7-cyclopropylmethyl-6-benz-[4,5]-isoxazoloxy)-butyloxy)phenylacetic acid;

4-(3-(3-Phenyl-7-propylbenzisoxazol-6-yloxy)propyloxy)-phenylacetic acid;

4-(3-(3-Phenyl-7-propylbenz[c]pyrazol-6-yloxy)propyloxy)-phenylacetic acid;

3-(4-(3-Phenyl-7-propylbenzisoxazol-6-yloxy)butyloxy)-phenylacetic acid;

3-(4-(3-Phenyl-7-propylbenz[c]pyrazol-6-yloxy)butyloxy)-phenylacetic acid;

4-(3-(3-Phenyl-7-propylbenzisoxazol-6-yloxy)propyloxy)-phenoxyacetic acid;

4-(3-(3-Phenyl-7-propylbenz[c]pyrazol-6-yloxy)propyloxy)-phenoxyacetic acid;

4-(3-(3-Phenyl-7-propylbenzisoxazol-6-yloxy)propylthio)-3-propylphenylacetic acid;

4-(4-(3-Phenyl-7-propylbenz[c]pyrazol-6-yloxy)butylthio)-3-chlorophenylacetic acid;

4-(4-(1-Phenyl-4-propylbenz[c]pyrazol-5-yloxy)butylthio)-3-chlorophenylacetic acid;

4-(3-(3-Phenyl-7-propylbenzisoxazol-6-yloxy)propylsulfonyl)-3-propylphenylacetic acid;

- 196 -

4-(3-(3-Phenyl-7-propylbenz[c]pyrazol-6-yloxy)propylsulfonyl)-3-chlorophenylacetic acid;

4-(4-(3-Phenyl-7-propylbenzisoxazol-6-yloxy)butylthio)-3-propylbenzyl-tetrazole;

4-(4-(3-Phenyl-7-propylindol-6-yloxy)butylthio)-3-chlorobenzyl-tetrazole;

4-(4-(1-Phenyl-4-propylindol-5-yloxy)butylthio)-3-chlorobenzyl-tetrazole;

4-(3-(3-Phenyl-7-propylbenzisoxazol-6-yloxy)propylamino)-phenylacetic acid;

4-(3-(3-Phenyl-7-propylbenz[c]pyrazol-6-yloxy)propylamino)-phenylacetic acid;

3-(4-(4-(3-Phenyl-7-propylbenzisoxazol-6-yloxy)butyloxy)-phenylacetic acid;

3-(4-(4-(3-Phenyl-7-propylbenz[c]pyrazol-6-yloxy)butyloxy)-phenylacetic acid;

3-chloro-4-(3-(2,2-dimethylpropyl)-7-(n-propyl)-6-benz[4,5]isoxazoloxy)-propylthio)phenylacetic acid;

3-Propyl-4-(3-(3-ethyl-7-propyl-6-benz-[4,5]-isoxazoloxy)-propyloxy)phenylacetic acid;

4-(3-(3-(Ethyl)-7-propyl-6-benz-[4,5]-isoxazoloxy)butyl)phenylacetate;

3-chloro-4-(7-(n-propyl)-3-(3,3,3-trifluoropropyl)-6-benz[4,5]isoxazoloxy)propylthio)phenylacetic acid;

- 197 -

3-chloro-4-(3-(3-trifluoromethyl-7-propyl-6-benz-[4, 5]-isoxazoloxy)propylamino)phenylacetic acid;

-Chloro-4-(3-(3-phenyl-7-propyl-6-benz-[4,5]-isoxazoloxy)-propylsulfoxy)phenylacetic acid;

3-fluoro-4-(4-(3-phenyl-7-propyl-6-benz-[4, 5]-isoxazoloxy)-butyloxy)phenylacetic acid;

3-chloro-4-(3-(2-phenylethyl)-7-propyl-6-benz[4,5]isoxazoloxy)propylthio)phenylacetic acid;

3-Chloro-4-(3-(3-(4-fluorophenyl)-7-propyl-6-benz-[4,5]-isoxazoloxy)-propylthio)phenylacetic acid;

3-Chloro-4-(3-(3-(4-fluorophenyl)-7-propyl-6-benz-[4,5]-isoxazoloxy)-propylsulfonyl)) phenylacetic acid;

2,3-Dichloro-4-(3-(3-neo-pental-7-propyl-6-benz-[4,5]-isoxazoloxy)-propylthio)phenylacetic acid;

2-(3-chloro-4-(3-(3-ethyl-7-propyl-6-benz-[4,5]-isoxazoloxy)propylthio)) phenylpropionic acid;

3-(4-(3-(3-phenyl-7-propyl-6-benz-[4,5]-isoxazoloxy)propyloxy)) phenylpropionic acid;

3-Chloro-4-(3-(3-(3-fluorophenyl)-7-propyl-6-benz-[4,5]-isoxazoloxy)-propylthio)phenylacetic acid;

4-(3-(3-phenyl-7-propyl-6-benz[4,5]isoxazole)oxy)propyloxy phenoxy acetic acid;

(3-(4-(3-phenyl-7-propyl-6-benz-[4,5]-isoxazoloxy)butyloxy)) phenylacetic acid;

- 198 -

3-(4-(4-(3-phenyl-7-propyl-6-benz-[4,5]-isoxazoloxy)butyloxy))
phenylpropionic acid;

3-chloro-4-(3-(2-methyl-2-phenylpropyl)-7-(n-propyl)-6-benz[4,5]isox-
azoloxy)propylthio)phenylacetic acid;

3-(4-(2-(3-phenyl-7-propyl-6-benz-[4,5]-isoxazoloxy)ethyloxy))
phenylpropionic acid;

(3-(4-(3-phenyl-7-propyl-6-benz-[4,5]-isoxazoloxy)butyloxy))
phenoxyacetic acid;

E-(4-(3-(3-phenyl-7-propyl-6-benz[4,5]isoxazole)oxy)propyloxy)
cinnamic acid;

3-(3-(3-(3-phenyl-7-propyl-6-benz[4,5]isoxazole)oxy)propyloxy)
phenylpropionic acid;

2-(4-(3-(3-phenyl-7-propyl-6-benz-[4,5]-isoxazoloxy)propyloxy))
phenoxypionic acid;

2-(4-(4-(3-phenyl-7-propyl-6-benz-[4,5]-isoxazoloxy)butyloxy))
phenoxypionic acid;

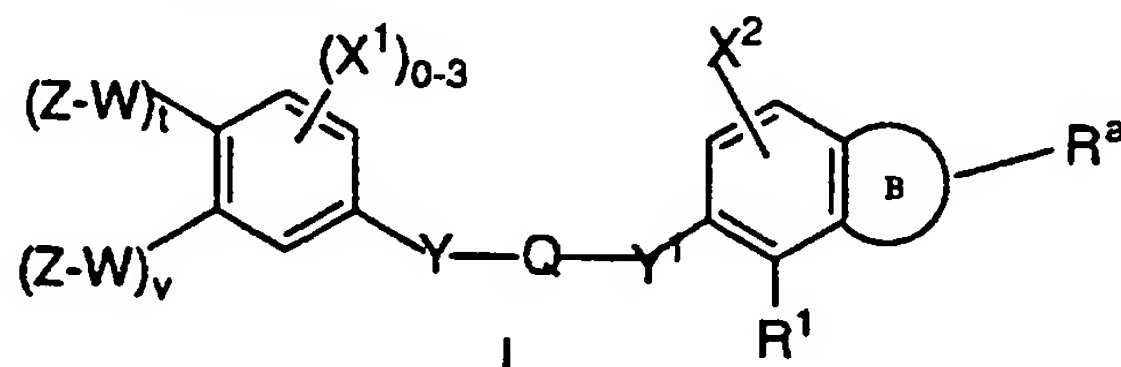
3-chloro-4-(3-(7-cyclopropylmethyl-3-phenyl-6-benz-[4, 5]-
isoxazoloxy)propyl-thio)phenylacetic acid;

1-(3-chloro-4-(3-(3-(2,2-dimethylpropyl)-7-propyl-6-
benz[4,5]isoxazole)oxy)propylthio) phenyl cyclopropane carboxylic
acid; and

4-(3-(3-(Ethyl)-7-(phenyl)-6-benz-[4,5]-isoxazoloxy)propyloxy)-3-
chloro- α , α -dimethyl-phenyl propionic acid.

- 199 -

15. A method for the treatment or prevention of diabetes which comprises administering to a diabetic patient an effective amount of a compound of formula I.



or a pharmaceutically acceptable salt thereof, wherein:

R is selected from the group consisting of H, C₁₋₆ alkyl, C₅₋₁₀ aryl, and C₅₋₁₀ heteroaryl, said alkyl, aryl and heteroaryl optionally substituted with 1 to 3 groups of R^a;

R¹ is selected from a group consisting of: H, C₁₋₁₅ alkyl, C₂₋₁₅ alkenyl, C₂₋₁₅ alkynyl and C₃₋₁₀ cycloalkyl, said alkyl, alkenyl, alkynyl, and cycloalkyl optionally substituted with 1 to 3 groups of R^a;

R³ is selected from a group consisting of: H, NHR¹, NHacyl, C₁₋₁₅ alkyl, C₃₋₁₀ cycloalkyl, C₂₋₁₅ alkenyl, C₁₋₁₅ alkoxy, CO₂alkyl, OH, C₂₋₁₅ alkynyl, C₅₋₁₀ aryl, C₅₋₁₀ heteroaryl said alkyl, cycloalkyl, alkenyl, alkynyl, aryl and heteroaryl optionally substituted with 1 to 3 groups of R^a;

(Z-W-) is Z-CR⁶R⁷-, Z-CH=CH-, or $Z-\overset{\overset{R^6}{\diagup}}{\underset{\diagdown}{C}}-R^8-$;

R⁸ is selected from the group consisting of CR⁶R⁷, O, NR⁶, and S(O)_p;

R⁶ and R⁷ are independently selected from the group consisting of H, C₁₋₆ alkyl;

- 200 -

B is a 5 or 6 membered heterocycle containing 0 to 2 double bonds, and 2 heteroatoms independently selected from the group consisting of O, N and S, said heteroatoms are optionally substituted at any position on the five or six membered heterocycle, the heterocycle being optionally unsubstituted or substituted with 1 to 3 groups of R^a ;

X^1 and X^2 are independently selected from a group consisting of: H, OH, C₁₋₁₅ alkyl, C₂₋₁₅ alkenyl, C₂₋₁₅ alkynyl, halo, OR^3 , $ORCF_3$, C₅₋₁₀ aryl, C₅₋₁₀ aralkyl, C₅₋₁₀ heteroaryl and C₁₋₁₀ acyl, said alkyl, alkenyl, alkynyl, aryl and heteroaryl optionally substituted with 1 to 3 groups of R^a ;

R^a represents a member selected from the group consisting of: halo, acyl, aryl, heteroaryl, CF_3 , OCF_3 , CN, NO_2 , R^3 , OR^3 , SR^3 , $S(O)R^3$, $=N(OR)$, SO_2R^3 , NR^3R^3 , NR^3COR^3 , $NR^3CO_2R^3$, $NR^3CON(R^3)_2$, $NR^3SO_2R^3$, COR^3 , CO_2R^3 , $CON(R^3)_2$, $SO_2N(R^3)_2$, $OCON(R^3)_2$ said aryl and heteroaryl optionally substituted with 1 to 3 groups of halo or C₁₋₆ alkyl;

Y is selected from the group consisting of: $S(O)_p$, $-CH_2-$, $-C(O)-$, $-C(O)NH-$, $-NR-$, $-O-$, $-SO_2NH$, $-NHSO_2$;

Y^1 is selected from the group consisting of: O and C;

Z is selected from the group consisting of: CO_2R^3 , $CONHSO_2R$, $CONH_2$ and 5-(1H-tetrazole);

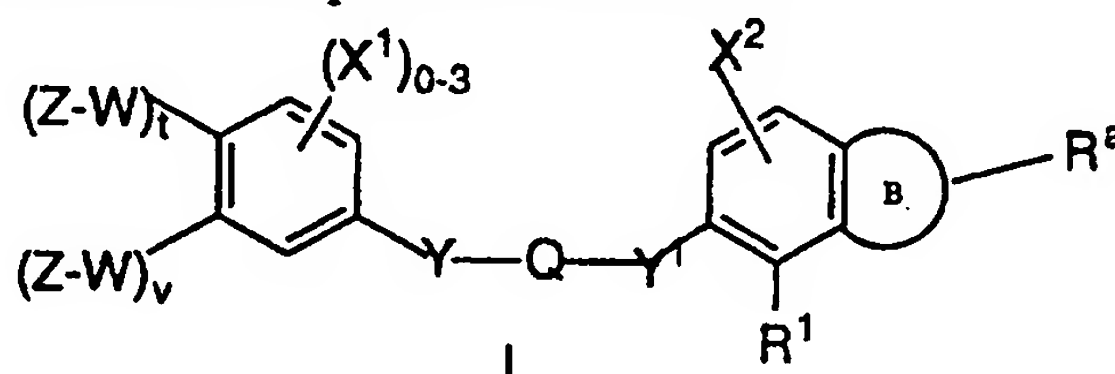
t and v are independently 0 or 1 such that $t + v = 1$;

Q is a saturated or unsaturated straight chain hydrocarbon containing 2-4 carbon atoms and

p is 0-2.

- 201 -

16. A method for lowering triglyceride levels which comprises administering to a patient needing lower triglyceride levels an effective amount of a compound of formula I.



or a pharmaceutically acceptable salt thereof, wherein:

R is selected from the group consisting of H, C₁₋₆ alkyl, C₅₋₁₀ aryl, and C₅₋₁₀ heteroaryl, said alkyl, aryl and heteroaryl optionally substituted with 1 to 3 groups of R^a;

R¹ is selected from a group consisting of: H, C₁₋₁₅ alkyl, C₂₋₁₅ alkenyl, C₂₋₁₅ alkynyl and C₃₋₁₀ cycloalkyl, said alkyl, alkenyl, alkynyl, and cycloalkyl optionally substituted with 1 to 3 groups of R^a;

R³ is selected from a group consisting of: H, NHR¹, NHacyl, C₁₋₁₅ alkyl, C₃₋₁₀ cycloalkyl, C₂₋₁₅ alkenyl, C₁₋₁₅ alkoxy, CO₂alkyl, OH, C₂₋₁₅ alkynyl, C₅₋₁₀ aryl, C₅₋₁₀ heteroaryl said alkyl, cycloalkyl, alkenyl, alkynyl, aryl and heteroaryl optionally substituted with 1 to 3 groups of R^a;

(Z-W-) is Z-CR⁶R⁷-, Z-CH=CH-, or $Z-\overset{\overset{R^6}{\diagup}}{\underset{\diagdown}{C}}-R^8-$;

R⁸ is selected from the group consisting of CR⁶R⁷, O, NR⁶, and S(O)_p;

R⁶ and R⁷ are independently selected from the group consisting of H, C₁₋₆ alkyl;

- 202 -

B is a 5 or 6 membered heterocycle containing 0 to 2 double bonds, and 2 heteroatoms independently selected from the group consisting of O, N and S, said heteroatoms are optionally substituted at any position on the five or six membered heterocycle, the heterocycle being optionally unsubstituted or substituted with 1 to 3 groups of R^a ;

X^1 and X^2 are independently selected from a group consisting of: H, OH, C1-15 alkyl, C2-15 alkenyl, C2-15 alkynyl, halo, OR^3 , $ORCF_3$, C5-10 aryl, C5-10 aralkyl, C5-10 heteroaryl and C1-10 acyl, said alkyl, alkenyl, alkynyl, aryl and heteroaryl optionally substituted with 1 to 3 groups of R^a ;

R^a represents a member selected from the group consisting of: halo, acyl, aryl, heteroaryl, CF_3 , OCF_3 , CN, NO_2 , R^3 , OR^3 , SR^3 , $S(O)R^3$, $=N(OR)$, SO_2R^3 , NR^3R^3 , NR^3COR^3 , $NR^3CO_2R^3$, $NR^3CON(R^3)_2$, $NR^3SO_2R^3$, COR^3 , CO_2R^3 , $CON(R^3)_2$, $SO_2N(R^3)_2$, $OCON(R^3)_2$ said aryl and heteroaryl optionally substituted with 1 to 3 groups of halo or C1-6 alkyl;

Y is selected from the group consisting of: $S(O)_p$, $-CH_2-$, $-C(O)-$, $-C(O)NH-$, $-NR-$, $-O-$, $-SO_2NH$, $-NHSO_2$;

Y^1 is selected from the group consisting of: O and C;

Z is selected from the group consisting of: CO_2R^3 , $CONHSO_2R$, $CONH_2$ and 5-(1H-tetrazole);

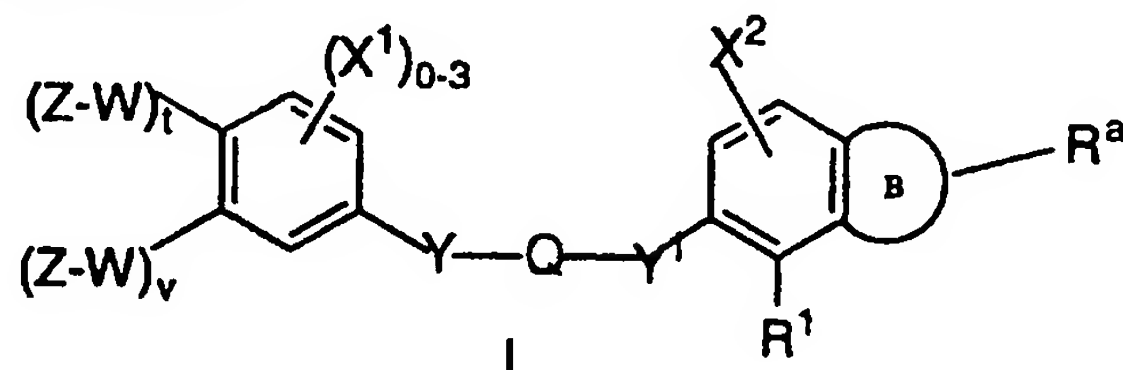
t and v are independently 0 or 1 such that $t + v = 1$;

Q is a saturated or unsaturated straight chain hydrocarbon containing 2-4 carbon atoms and

p is 0-2.

- 203 -

17. A method for treating obesity which comprises administering to a patient in need thereof an effective amount of a compound of formula I.



or a pharmaceutically acceptable salt thereof, wherein:

R is selected from the group consisting of H, C₁-6 alkyl, C₅-10 aryl, and C₅-10 heteroaryl, said alkyl, aryl and heteroaryl optionally substituted with 1 to 3 groups of R^a;

R¹ is selected from a group consisting of: H, C₁-15 alkyl, C₂-15 alkenyl, C₂-15 alkynyl and C₃-10 cycloalkyl, said alkyl, alkenyl, alkynyl, and cycloalkyl optionally substituted with 1 to 3 groups of R^a;

R³ is selected from a group consisting of: H, NHR¹, NHacyl, C₁-15 alkyl, C₃-10 cycloalkyl, C₂-15 alkenyl, C₁-15 alkoxy, CO₂alkyl, OH, C₂-15 alkynyl, C₅-10 aryl, C₅-10 heteroaryl said alkyl, cycloalkyl, alkenyl, alkynyl, aryl and heteroaryl optionally substituted with 1 to 3 groups of R^a;

(Z-W-) is Z-CR⁶R⁷-, Z-CH=CH-, or $\text{Z}-\text{C}(\text{R}^6)(\text{R}^7)-\text{R}^8-$;

R⁸ is selected from the group consisting of CR⁶R⁷, O, NR⁶, and S(O)_p;

R⁶ and R⁷ are independently selected from the group consisting of H, C₁₋₆ alkyl;

- 204 -

B is a 5 or 6 membered heterocycle containing 0 to 2 double bonds, and 2 heteroatoms independently selected from the group consisting of O, N and S, said heteroatoms are optionally substituted at any position on the five or six membered heterocycle, the heterocycle being optionally unsubstituted or substituted with 1 to 3 groups of R^a ;

X^1 and X^2 are independently selected from a group consisting of: H, OH, C1-15 alkyl, C2-15 alkenyl, C2-15 alkynyl, halo, OR^3 , $ORCF_3$, C5-10 aryl, C5-10 aralkyl, C5-10 heteroaryl and C1-10 acyl, said alkyl, alkenyl, alkynyl, aryl and heteroaryl optionally substituted with 1 to 3 groups of R^a ;

R^a represents a member selected from the group consisting of: halo, acyl, aryl, heteroaryl, CF_3 , OCF_3 , CN, NO_2 , R^3 , OR^3 , SR^3 , $S(O)R^3$, $=N(OR)$, SO_2R^3 , NR^3R^3 , NR^3COR^3 , $NR^3CO_2R^3$, $NR^3CON(R^3)_2$, $NR^3SO_2R^3$, COR^3 , CO_2R^3 , $CON(R^3)_2$, $SO_2N(R^3)_2$, $OCON(R^3)_2$ said aryl and heteroaryl optionally substituted with 1 to 3 groups of halo or C1-6 alkyl;

Y is selected from the group consisting of: $S(O)_p$, $-CH_2-$, $-C(O)-$, $-C(O)NH-$, $-NR-$, $-O-$, $-SO_2NH$, $-NH SO_2$;

Y^1 is selected from the group consisting of: O and C;

Z is selected from the group consisting of: CO_2R^3 , $CONHSO_2R$, $CONH_2$ and 5-(1H-tetrazole);

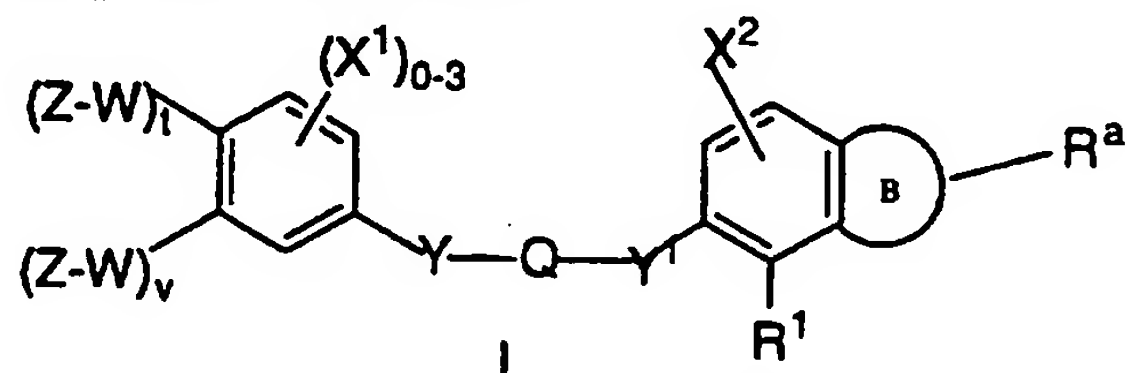
t and v are independently 0 or 1 such that $t + v = 1$;

Q is a saturated or unsaturated straight chain hydrocarbon containing 2-4 carbon atoms and

p is 0-2.

- 205 -

18. A method for treating atherosclerosis or reducing the risk of developing atherosclerosis or having an atherosclerotic disease event comprising the administration to a mammal at risk of developing atherosclerosis or having an atherosclerotic disease event of an effective amount of a compound of formula I



or a pharmaceutically acceptable salt thereof, wherein:

R is selected from the group consisting of H, C₁-6 alkyl, C₅-10 aryl, and C₅-10 heteroaryl, said alkyl, aryl and heteroaryl optionally substituted with 1 to 3 groups of R^a;

R¹ is selected from a group consisting of: H, C₁-15 alkyl, C₂-15 alkenyl, C₂-15 alkynyl and C₃-10 cycloalkyl, said alkyl, alkenyl, alkynyl, and cycloalkyl optionally substituted with 1 to 3 groups of R^a;

R³ is selected from a group consisting of: H, NHR¹, NHacyl, C₁-15 alkyl, C₃-10 cycloalkyl, C₂-15 alkenyl, C₁-15 alkoxy, CO₂alkyl, OH, C₂-15 alkynyl, C₅-10 aryl, C₅-10 heteroaryl said alkyl, cycloalkyl, alkenyl, alkynyl, aryl and heteroaryl optionally substituted with 1 to 3 groups of R^a;

(Z-W-) is Z-CR⁶R⁷-, Z-CH=CH-, or $Z-\overset{\overset{R^6}{\diagup}}{\underset{\diagdown}{C}}-R^8-$;

R⁸ is selected from the group consisting of CR⁶R⁷, O, NR⁶, and S(O)_p;

- 206 -

R^6 and R^7 are independently selected from the group consisting of H, C_{1-6} alkyl;

B is a 5 or 6 membered heterocycle containing 0 to 2 double bonds, and 2 heteroatoms independently selected from the group consisting of O, N and S, said heteroatoms are optionally substituted at any position on the five or six membered heterocycle, the heterocycle being optionally unsubstituted or substituted with 1 to 3 groups of R^a ;

X^1 and X^2 are independently selected from a group consisting of: H, OH, C_{1-15} alkyl, C_{2-15} alkenyl, C_{2-15} alkynyl, halo, OR^3 , $ORCF_3$, C_{5-10} aryl, C_{5-10} aralkyl, C_{5-10} heteroaryl and C_{1-10} acyl, said alkyl, alkenyl, alkynyl, aryl and heteroaryl optionally substituted with 1 to 3 groups of R^a ;

R^a represents a member selected from the group consisting of: halo, acyl, aryl, heteroaryl, CF_3 , OCF_3 , CN, NO_2 , R^3 , OR^3 ; SR^3 , $S(O)R^3$, $=N(OR)$, SO_2R^3 , NR^3R^3 , NR^3COR^3 , $NR^3CO_2R^3$, $NR^3CON(R^3)_2$, $NR^3SO_2R^3$, COR^3 , CO_2R^3 , $CON(R^3)_2$, $SO_2N(R^3)_2$, $OCON(R^3)_2$ said aryl and heteroaryl optionally substituted with 1 to 3 groups of halo or C_{1-6} alkyl;

Y is selected from the group consisting of: $S(O)_p$, $-CH_2-$, $-C(O)-$, $-C(O)NH-$, $-NR-$, $-O-$, $-SO_2NH$, $-NH SO_2$;

Y^1 is selected from the group consisting of: O and C;

Z is selected from the group consisting of: CO_2R^3 , $CONHSO_2R$, $CONH_2$ and 5-(1H-tetrazole);

t and v are independently 0 or 1 such that $t + v = 1$;

Q is a saturated or unsaturated straight chain hydrocarbon containing 2-

- 207 -

carbon atoms and

p is 0-2.

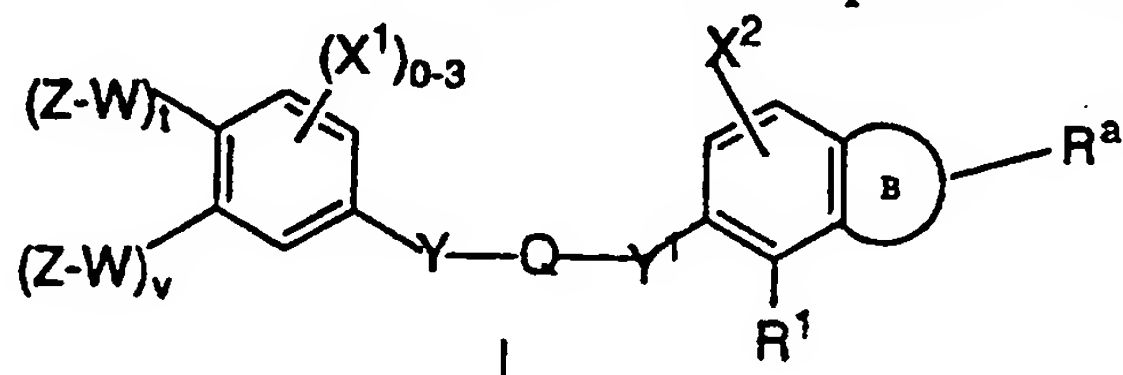
19. A method according to claim 18 wherein the compound has an IC₅₀ equal to or less than 10 μ M in the hPPAR δ binding assay and an EC₅₀ equal to or less than 10 μ M in the hPPAR δ transactivation assay.

20. The method of Claim 19 wherein the compound has an IC₅₀ equal to or less than 100 nM in the hPPAR δ binding assay and an EC₅₀ equal to or less than 100 nM in the hPPAR δ transactivation assay.

21. The method of Claim 20 wherein the compound has an IC₅₀ equal to or less than 50 nM in the hPPAR δ binding assay and an EC₅₀ equal to or less than 50 nM in the hPPAR δ transactivation assay.

22. The method of Claim 21 wherein the compound has an IC₅₀ equal to or less than 10 nM in the hPPAR δ binding assay and an EC₅₀ equal to or less than 10 nM in the hPPAR δ transactivation assay.

23. A method for raising high density lipoprotein plasma levels in a mammal in need of such treatment, comprising the administration of an effective amount of a compound of formula I.



or a pharmaceutically acceptable salt thereof, wherein:

- 208 -

R is selected from the group consisting of H, C₁₋₆ alkyl, C₅₋₁₀ aryl, and C₅₋₁₀ heteroaryl, said alkyl, aryl and heteroaryl optionally substituted with 1 to 3 groups of R^a;

R¹ is selected from a group consisting of: H, C₁₋₁₅ alkyl, C₂₋₁₅ alkenyl, C₂₋₁₅ alkynyl and C₃₋₁₀ cycloalkyl, said alkyl, alkenyl, alkynyl, and cycloalkyl optionally substituted with 1 to 3 groups of R^a;

R³ is selected from a group consisting of: H, NHR¹, NHacyl, C₁₋₁₅ alkyl, C₃₋₁₀ cycloalkyl, C₂₋₁₅ alkenyl, C₁₋₁₅ alkoxy, CO₂alkyl, OH, C₂₋₁₅ alkynyl, C₅₋₁₀ aryl, C₅₋₁₀ heteroaryl said alkyl, cycloalkyl, alkenyl, alkynyl, aryl and heteroaryl optionally substituted with 1 to 3 groups of R^a;

(Z-W-) is Z-CR⁶R⁷-, Z-CH=CH-, or $\begin{array}{c} \text{R}^6 \quad \text{R}^7 \\ \diagdown \quad \diagup \\ \text{Z}-\text{C}-\text{R}^8- \end{array}$;

R⁸ is selected from the group consisting of CR⁶R⁷, O, NR⁶, and S(O)_p;

R⁶ and R⁷ are independently selected from the group consisting of H, C₁₋₆ alkyl;

B is a 5 or 6 membered heterocycle containing 0 to 2 double bonds, and 2 heteroatoms independently selected from the group consisting of O, N and S, said heteroatoms are optionally substituted at any position on the five or six membered heterocycle, the heterocycle being optionally unsubstituted or substituted with 1 to 3 groups of R^a;

X¹ and X² are independently selected from a group consisting of: H, OH, C₁₋₁₅ alkyl, C₂₋₁₅ alkenyl, C₂₋₁₅ alkynyl, halo, OR³, ORCF₃, C₅₋₁₀ aryl, C₅₋₁₀ aralkyl, C₅₋₁₀ heteroaryl and C₁₋₁₀ acyl, said alkyl, alkenyl, alkynyl, aryl and heteroaryl optionally substituted with 1 to 3 groups of R^a;

- 209 -

R^a represents a member selected from the group consisting of: halo, acyl, aryl, heteroaryl, CF₃, OCF₃, CN, NO₂, R³, OR³, SR³, S(O)R³, =N(OR), SO₂R³, NR³R³, NR³COR³, NR³CO₂R³, NR³CON(R³)₂, NR³SO₂R³, COR³, CO₂R³, CON(R³)₂, SO₂N(R³)₂, OCON(R³)₂ said aryl and heteroaryl optionally substituted with 1 to 3 groups of halo or C1-6 alkyl;

Y is selected from the group consisting of: S(O)_p, -CH₂-, -C(O)-, -C(O)NH-, -NR-, -O-, -SO₂NH-, -NHSO₂;

Y¹ is selected from the group consisting of: O and C;

Z is selected from the group consisting of: CO₂R³, CONHSO₂R, CONH₂ and 5-(1H-tetrazole);

t and v are independently 0 or 1 such that t + v = 1;

Q is a saturated or unsaturated straight chain hydrocarbon containing 2-4 carbon atoms and

p is 0-2.

24. A method according to claim 23 wherein the compound has an IC₅₀ equal to or less than 10 μM in the hPPARδ binding assay and an EC₅₀ equal to or less than 10 μM in the hPPARδ transactivation assay.

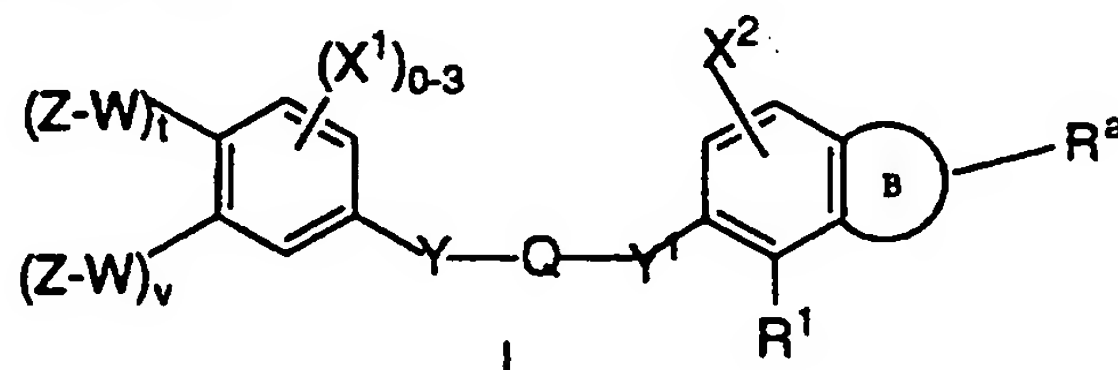
25. The method of Claim 24 wherein the compound has an IC₅₀ equal to or less than 100 nM in the hPPARδ binding assay and an EC₅₀ equal to or less than 100 nM in the hPPARδ transactivation assay.

- 210 -

26. The method of Claim 25 wherein the compound has an IC₅₀ equal to or less than 50 nM in the hPPAR δ binding assay and an EC₅₀ equal to or less than 50 nM in the hPPAR δ transactivation assay.

27. The method of Claim 26 wherein the compound has an IC₅₀ equal to or less than 10 nM in the hPPAR δ binding assay and an EC₅₀ equal to or less than 10 nM in the hPPAR δ transactivation assay.

28. A post-myocardial infarction therapy comprising administering to a human who has suffered a myocardial infarction a compound of formula I.



or a pharmaceutically acceptable salt thereof, wherein:

R is selected from the group consisting of H, C₁-6 alkyl, C₅-10 aryl, and C₅-10 heteroaryl, said alkyl, aryl and heteroaryl optionally substituted with 1 to 3 groups of R^a;

R¹ is selected from a group consisting of: H, C₁-15 alkyl, C₂-15 alkenyl, C₂-15 alkynyl and C₃-10 cycloalkyl, said alkyl, alkenyl, alkynyl, and cycloalkyl optionally substituted with 1 to 3 groups of R^a;

R³ is selected from a group consisting of: H, NHR¹, NHacyl, C₁-15 alkyl, C₃-10 cycloalkyl, C₂-15 alkenyl, C₁-15 alkoxy, CO₂alkyl, OH, C₂-15 alkynyl, C₅-10 aryl, C₅-10 heteroaryl said alkyl, cycloalkyl, alkenyl, alkynyl, aryl and heteroaryl optionally substituted with 1 to 3 groups of R^a;

(Z-W-) is Z-CR⁶R⁷-, Z-CH=CH-, or $\text{Z}-\text{C} \begin{matrix} \text{R}^6 & \text{R}^7 \\ \diagup & \diagdown \end{matrix} -\text{R}^a-$;

- 211 -

R^8 is selected from the group consisting of CR^6R^7 , O, NR^6 , and $S(O)_p$;

R^6 and R^7 are independently selected from the group consisting of H, C_{1-6} alkyl;

B is a 5 or 6 membered heterocycle containing 0 to 2 double bonds, and 2 heteroatoms independently selected from the group consisting of O, N and S, said heteroatoms are optionally substituted at any position on the five or six membered heterocycle, the heterocycle being optionally unsubstituted or substituted with 1 to 3 groups of R^a ;

X^1 and X^2 are independently selected from a group consisting of: H, OH, C_{1-15} alkyl, C_{2-15} alkenyl, C_{2-15} alkynyl, halo, OR^3 , $ORCF_3$, C_{5-10} aryl, C_{5-10} aralkyl, C_{5-10} heteroaryl and C_{1-10} acyl, said alkyl, alkenyl, alkynyl, aryl and heteroaryl optionally substituted with 1 to 3 groups of R^a ;

R^a represents a member selected from the group consisting of: halo, acyl, aryl, heteroaryl, CF_3 , OCF_3 , CN, NO_2 , R^3 , OR^3 , SR^3 , $S(O)R^3$, $=N(OR)$, SO_2R^3 , NR^3R^3 , NR^3COR^3 , $NR^3CO_2R^3$, $NR^3CON(R^3)_2$, $NR^3SO_2R^3$, COR^3 , CO_2R^3 , $CON(R^3)_2$, $SO_2N(R^3)_2$, $OCON(R^3)_2$ said aryl and heteroaryl optionally substituted with 1 to 3 groups of halo or C_{1-6} alkyl;

Y is selected from the group consisting of: $S(O)_p$, $-CH_2-$, $-C(O)-$, $-C(O)NH-$, $-NR-$, $-O-$, $-SO_2NH$, $-NHSO_2$;

Y^1 is selected from the group consisting of: O and C;

Z is selected from the group consisting of: CO_2R^3 , $CONHSO_2R$, $CONH_2$ and 5-(1H-tetrazole);

- 212 -

t and v are independently 0 or 1 such that $t + v = 1$;

Q is a saturated or unsaturated straight chain hydrocarbon containing 2-4 carbon atoms and

p is 0-2.

29. A method according to claim 28 wherein the compound has an IC₅₀ equal to or less than 10 μ M in the hPPAR δ binding assay and an EC₅₀ equal to or less than 10 μ M in the hPPAR δ transactivation assay.

30. The method of Claim 29 wherein the compound has an IC₅₀ equal to or less than 100 nM in the hPPAR δ binding assay and an EC₅₀ equal to or less than 100 nM in the hPPAR δ transactivation assay.

31. The method of Claim 30 wherein the compound has an IC₅₀ equal to or less than 50 nM in the hPPAR δ binding assay and an EC₅₀ equal to or less than 50 nM in the hPPAR δ transactivation assay.

32. The method of Claim 31 wherein the compound has an IC₅₀ equal to or less than 10 nM in the hPPAR δ binding assay and an EC₅₀ equal to or less than 10 nM in the hPPAR δ transactivation assay.

33. A method for the treatment or prevention of diabetes which comprises administering to a diabetic patient an effective amount of a compound of Claim 15 in combination with a sulfonylurea, fibrate, HMG-CoA reductase inhibitor, beta-sitosterol inhibitor, cholesterol acyltransferase inhibitor, biguanides, cholestyramine, angiotensin II antagonist, melinamide, nicotinic acid, fibrinogen receptor antagonists, aspirin, α -glucosidase inhibitors, insulin secretagogue or insulin.

- 213 -

34. A method for halting, preventing or reducing the risk of developing atherosclerosis and related disease events which comprises administering to a patient in need thereof an effective amount of a compound of Claim 18 in combination with a sulfonylurea, fibrate, HMG-CoA reductase inhibitor, beta-sitosterol inhibitor, cholesterol acyltransferase inhibitor, biguanides, cholestyramine, angiotensin II antagonist, melinamide, nicotinic acid, fibrinogen receptor antagonists, aspirin, α -glucosidase inhibitors, insulin secretagogue or insulin.

35. A method according to claim 34 wherein the compound has an IC₅₀ equal to or less than 10 μ M in the hPPAR δ binding assay and an EC₅₀ equal to or less than 10 μ M in the hPPAR δ transactivation assay.

36. The method of Claim 35 wherein the compound has an IC₅₀ equal to or less than 100 nM in the hPPAR δ binding assay and an EC₅₀ equal to or less than 100 nM in the hPPAR δ transactivation assay.

37. The method of Claim 36 wherein the compound has an IC₅₀ equal to or less than 50 nM in the hPPAR δ binding assay and an EC₅₀ equal to or less than 50 nM in the hPPAR δ transactivation assay.

38. The method of Claim 37 wherein the compound has an IC₅₀ equal to or less than 10 nM in the hPPAR δ binding assay and an EC₅₀ equal to or less than 10 nM in the hPPAR δ transactivation assay.

39. A method for the treatment or prevention of obesity which comprises administering to an obese patient an effective amount of a compound of Claim 16 in combination with a fenfluramine, dexfenfluramine, phentiramine or β ₃ adrenergic receptor agonist.

40. A composition for the treatment of diabetes or for lowering triglyceride levels or for halting, preventing or reducing the

- 214 -

risk of developing atherosclerosis and related disease events, or for raising high density lipoprotein plasma levels, which comprises an inert carrier and an effective amount of a compound of Claim 1.

41. A composition for the treatment of diabetes which comprises an inert carrier and an effective amount of a compound of Claim 1, in combination with a sulfonylurea, fibrate, HMG-CoA reductase inhibitor, beta-sitosterol inhibitor, cholesterol acyltransferase inhibitor, biguanides, cholestyramine, angiotensin II antagonist, melinamide, nicotinic acid, fibrinogen receptor antagonists, aspirin, α -glucosidase inhibitors, insulin secretagogue or insulin.

42. A composition for halting, preventing or reducing the risk of developing atherosclerosis and related disease events, or for raising high density lipoprotein plasma levels, which comprises an inert carrier and an effective amount of a compound of Claim 1, in combination with a sulfonylurea, fibrate, HMG-CoA reductase inhibitor, beta-sitosterol inhibitor, cholesterol acyltransferase inhibitor, biguanides, cholestyramine, angiotensin II antagonist, melinamide, nicotinic acid, fibrinogen receptor antagonists, aspirin, α -glucosidase inhibitors, insulin secretagogue or insulin.

43. A method according to claim 42 wherein the compound has an IC_{50} equal to or less than $10\ \mu M$ in the hPPAR δ binding assay and an EC_{50} equal to or less than $10\ \mu M$ in the hPPAR δ transactivation assay.

44. The method of Claim 43 wherein the compound has an IC_{50} equal to or less than $100\ nM$ in the hPPAR δ binding assay and an EC_{50} equal to or less than $100\ nM$ in the hPPAR δ transactivation assay.

- 215 -

45. The method of Claim 44 wherein the compound has an IC₅₀ equal to or less than 50 nM in the hPPAR δ binding assay and an EC₅₀ equal to or less than 50 nM in the hPPAR δ transactivation assay.

46. The method of Claim 45 wherein the compound has an IC₅₀ equal to or less than 10 nM in the hPPAR δ binding assay and an EC₅₀ equal to or less than 10 nM in the hPPAR δ transactivation assay.

47. A composition for the treatment of obesity which comprises an inert carrier and an effective amount of a compound of Claim 1, in combination with a fenfluramine, dexfenfluramine, phentiramine or β ₃ adrenergic receptor agonist.

INTERNATIONAL SEARCH REPORT

Inter. Application No

PCT/US 97/01749

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07D261/20 C07D275/04 A61K31/42 A61K31/425 C07D263/56
C07D231/56 C07D249/18 C07D239/74 A61K31/505 A61K31/415
A61K31/41

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 611 003 A (MERCK & CO INC) 17 August 1994 see claims -----	1,15-47

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *Z* document member of the same patent family

Date of the actual completion of the international search

14 April 1997

Date of mailing of the international search report

21.04.97

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+ 31-70) 340-3016

Authorized officer

Henry, J

INTERNATIONAL SEARCH REPORT

national application No.

PCT/US 97/01749

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 15-47 are directed to a method of treatment of the human body the search has been carried out and based on the alleged effects of the compounds.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int. Application No

PCT/US 97/01749

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0611003 A	17-08-94	US 5451677 A	19-09-95
		AU 670477 B	18-07-96
		AU 5498694 A	29-06-95
		CA 2114712 A	10-08-94
		JP 7010827 A	13-01-95
		WO 9418161 A	18-08-94
		ZA 9400846 A	05-09-94
